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SYMPOSIUM ON INFLAMMATION

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Neurogenic inflammatory responses

Our investigations have clearly proved that cutaneous vascular permeability is subject to nervous control. Stimulation of sensory nerves is well-known to cause "antidromic vasodilatation." Our experiments demonstrate in addition that somatic sensory nerves are able to alter the permeability of the minute vessels. In rats pretreated with Evans blue, electrical stimulation of the n. saphenus induces an intensive blue colouration of the innervated skin. Presumably, under the influence of the stimulation, a mediator substance is released from the sensory nerve endings, which greatly enhances vascular permeability.

The same mechanism may also be activated by orthodromic stimulation of the sensory nerves. Thus, the permeability-increasing mediator substance may be liberated by excitation of the pain receptors with chemical irritants, too. It is easy to prove with denervation experiments that many well-known irritants (*e.g.* xylene, chloracetophenone, mustard oil) exert their inflammatory action in this way. In rats pretreated with Evans blue these irritants applied to the skin induce local dye accumulation. This dye accumulation is completely prevented by denervation, if severing of the sensory nerve is performed two or more days prior to the experiment.

According to the general view based on the work of BRUCE, BAYLISS and KROGH, such neurogenic inflammatory responses are brought about by an axon reflex. Our experiments, however, show that the above-mentioned inflammatory responses elicited in rats with chemical irritants can by no means be attributed to an axon reflex mechanism. A solution of capsaicin, chloracetophenone or mustard oil instilled into the rat's eye induces in the conjunctiva an intense blue dye exudation. This effect is neurogenic in nature since it does not occur after degeneration of the opthalmic branch of the n. trigeminus. The inflammatory effect is, however, not affected by previous local anaesthesia of the eye with cocaine, Cornecaine or Psicain-Neu. Since in these experiments the conductibility of the nerve fibres was completely abolished, an axon reflex cannot be involved in the mechanism of the inflammatory response.

This paradoxical finding can only be explained by the assumption that (i) pain receptors cannot be paralyzed by local anaesthetics; and (ii) chemical stimulants release the vasoactive mediator substance by a direct orthodromic stimulatory action from the pain receptors themselves and the mediator substance then gains access to the vessels by diffusion. This assumption is consistent with the well-known electrophysiological experience that sensory receptors are highly refractory to the action of local anaesthetics.

Experiments performed on rats desensitized with capsaicin strongly support the above conclusions. In previous investigations (JANCSÓ and JANCSÓ -GÁBOR, 1959) we have shown that repeated parenteral administration of capsaicin induces in rats and guinea pigs a peculiar sensory disturbance lasting weeks or even years. The animals become insensitive to pain by chemical substances, while the perception of pain caused by physical means remains unimpaired. Experiments in which the action potentials from the saphenous nerve were recorded clearly showed that capsaicin desensitization renders cutaneous pain receptors almost inexcitable by chemical stimuli. In recent experiments it could be established that in desensitized rats electrical stimulation of the saphenous nerve does not evoke Evans blue accumulation in the corresponding skin area. In all probability, the abolition of the effect of nerve stimulation is due to the failure of the nerve endings to release the permeability-increasing principle. Hence, capsaicin should be considered as a sensory neurone blocking agent which probably interferes with the synthesis of the mediator substance in the pain receptor, or in the whole neurone. It is quite possible that just this break-down of mediator production is responsible for the characteristic loss of chemo-sensitivity.

Since desensitized nerve endings do not produce the permeability increasing substance, orthodromic stimulation is also ineffective. Painting of the skin of the capsaicin-desensitized rat with xylene or with a solution of chloracetophenone or mustard oil does not cause a local accumulation of Evans blue. Similarly, there is no chemosis and dye exudation to be observed if capsaicin or other neurogenically acting inflammatory agents are instilled into the conjunctival sac.

Neurogenic inflammatory responses cannot be inhibited with atropine, physostigmine, hexamethonium, dibenamine, antihistamines and 5-hydroxytryptamine-antagonists. Pretreatment with prednisolone, however, greatly reduces local blue dye exudation caused by electrical stimulation of the saphenous nerve.

Skin extracts prepared after electrical stimulation of the nerve show an enhanced bradykinin-like activity on the rat uterus. This suggests that the mediator substance may be a bradykinin-like polypeptide, or the enzyme producing it.

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Chemical excitants of pain

The production of pain by chemical agents can be studied by application of solutions to the exposed base of a blister induced by cantharidin. In this preparation the subjective pain responses to different concentrations of active substances are consistent and pain is produced without stimulation of other sensory modalities in the skin.

Isotonic NaCl solution (0.9%) produces no pain; above 1.8% and below 0.45% NaCl solutions begin to cause pain, which is very severe at 6× isotonic or with distilled water. It is unlikely that changes in osmolarity should account for pathological pain.

Acids, such as HCl and lactic acids cause pain at pH values below 3—4. Acid buffer solutions cause pain at pH values up to 6.5. HCl in gastric juice at pH < 3 may contribute to the pain of peptic ulcer, and acid buffers to pain in areas of inflammation.

Potassium ions produce pain in concentrations exceeding 15—30 meq/litre. Such concentrations could be produced by the rapid escape of intracellular K^+ such as might occur in the necrosis of skeletal muscle induced by sea snake venom.

Acetylcholine produces pain in concentrations exceeding 10^{-5} g/ml, but there is no evidence that this substance mediates pathological pain.

Histamine usually causes itch in concentrations of 10^{-7}—10^{-5} g/ml, and in higher concentrations leads to pain followed by itch. Histamine release in the body is much more likely to cause itch than pain, *e.g.* in urticaria.

5-Hydroxytryptamine (5-HT, serotonin) causes pain in concentrations of 10^{-7} g/ml and above. Its release from disintegrating platelets could cause pain when blood comes into contact with damaged tissues.

Bradykinin and kallidin (which are described as plasma kinins) are polypeptides which are formed from plasma. They produce pain in concentrations of 10^{-7} g/ml and above. They also produce other features of inflammation such as vasodilatation, increased capillary permeability and migration of leucocytes. Plasma kinins can be formed (1) by the addition of plasma of extrinsic agents, such as trypsin, kallikrein and snake venoms, and (2) by activation of a complex intrinsic kinin-forming system present in plasma. This activation can be brought about by contact of plasma with foreign surfaces such as glass, and by treatment of plasma with acid or acetone. It seems likely that kinin formation is promoted when plasma comes into contact with damaged tissues, and also in axon reflex vasodilatation associated with hyperalgesia.

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Pathogenesis and biological significance of inflammatory oedema

Several years ago (cf. SCHADE) the development of inflammatory oedema was considered a passive consequence of the biophysical changes in irritated tissue. Our investigations showed that inflammatory oedema is a manifestation of an active reaction of the organism. Oedema occurs as a result of enhanced blood vessel permeability, increased exudation and of the delay of fluid outflow from inflamed tissue. Blood vessel permeability derangement develops soon after the influence of the irritant and under neurohormonal control.

The relative significance of different permeability factors changes with the character and strength of the inflammatory agents. For example, the participation of histamine and globulin permeability factors is relatively insignificant during oedema formation in inflammation caused by burn (54°C) of the rabbit's paw.

From the phylogenetical and ontogenetical point of view, exudation is a process younger than leucocytic emigration. In higher animals, exudation precedes leucocytic emigration and can be regarded as the first link in the protective physiological reaction during inflammation.

Inflammation leads to functional and morphological demarcation of the injured tissue from the organism which manifests itself in a decreased permeability from the inflammatory focus to the unaffected tissue, and *vice versa*. The mechanism of demarcation of the inflamed tissue and of formation of the functional barrier is a complex one. Of importance are the reduction of the blood and lymph flow, the binding of low molecular substances by proteins of the exudate, resulting in the formation of large complexes which are slowly absorbed, the development of granulation tissue, the phagocytic activity of micro- and macrophages, *etc.*

The role of fibrin in the barrier and fixing properties of normergic inflammation is not so important as claimed by MENKIN. With normergic inflammation fibrin deposition in tissue and vessels is not the cause of the decreased permeability and the barrier properties of the inflamed tissue. In general, blood clotting does not play a significant part in the early appearance of normergic inflammation. The anti-inflammatory action of Phlogodym (neodymium pyrocatechol disulphonate) synthetized by JANCSÓ, does not depend on the anticoagulant properties of this compound, as shown in rabbit experiments, and is perhaps a result of its direct influence on the blood vessels.

As distinct from normergic inflammation, intravascular blood clotting (fibrin deposition and thrombosis) is the most prominent link in the pathogenesis of hyperergic inflammation *(e.g.* Shwartzmann phenomenon).

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Inflammation and leucocytic phagocytosis

It has been shown that the phagocytic activity of leucocytes is stimulated more potently by an inflammatory exudate than by blood serum or transudate, the last-named factor being the least effective in this respect. Systematic studies have been undertaken to elucidate the physiological background of this phenomenon, and certain new aspects of the problem could be revealed. Antihistamine substances were found to inhibit the phagocytosis-promoting effect of exudates. Histamine in concentrations demonstrable in exudates enhanced the phagocytotic activity of leucocytes. Serotonin produced a similar effect. Protein hydrolysates (DEKANSKY), leucotaxin and exudin isolated from exudate according to MENKIN, strongly increased the phagocytic activity of leucocytes *in vitro*. MENKIN's leucocytosis promoting factor (LPF) stimulated leucocytic activity both *in vivo* and *in vitro*. The peak of the effect coincided with the peak of the leucocytosis produced. Leucopenin and the leucopenic factor (MENKIN) prepared from older acidotic exudates reduced the number of leucocytes and diminished at the same time the phagocytic activity of the cells. The phagocytotic activity of the leucocytes incubated with necrosin obtained from exudate, was definitely decreased. The fractions obtained from serum or transudate by methods similar to those used for isolating the secondary inflammatory stimulants of MENKIN, were ineffective. Leucocytic bacterium phagocytosis was enhanced by sodium ribo- and desoxyribonucleate, hyaluronidase, and bradykinine.

On the basis of the results, the phagocytosis-promoting effect of the exudate is a resultant of an interaction of several factors. Various biogenic substances are involved; these exert, apart a local effect, also distant actions starting from the area of inflammation. All this proves once again that a close interaction exists between the organism as a whole and the area of inflammation, demarcated more or less by the inflammatory barrier.

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Elimination of leucocytes from circulating blood

Paper not submitted.

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The effect of thyrotropic hormone on granulation tissue

Observing thyroidectomized patients it was noted that their skin wound healed with a keloid. Assuming a correlation between the thyroidectomized condition and the increased connective tissue proliferation in the granulation tissue, we studied the question in animals by SELYE's method somewhat modified by us. Croton oil was injected into a dorsal skin pouch of rats and the weight and histology of the granulation tissue thus produced, the quantity of exudate in the pouch as well as the concentration of total protein and of glucosamine-HCl was examined. Significant differences have been found between the controls, the thyroidectomized animals with increased TSH secretion and those treated locally with TSH. According to the results, thyroidectomy increases the amount of granulation tissue, makes the skin more sensitive to necrosis, changes the quality of the exudate, and enhances inflammation.

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Effects of anti-inflammatory substances on the fluorescein permeability of the blood-aqueous humour barrier

Most of the methods applied for investigating the permeability of minute vessels induce by themselves inflammation and/or histamine release in the area studied. The slit-lamp method of AMSLER measuring the fluorescein permeability of the blood-aqueous humour barrier of the eye indicates non-inflammatory permeability and very probably does not cause histamine liberation, so it seems therefore to allow some interesting comparisons. Recent literature also tends to separate inflammatory and non-inflammatory permeability.

In the present experiments it was studied in rats, how the amount of fluorescein in the aqueous humour was changed following the administration of sodium salicylate, butazolidine, prednisolone and Sandosten-calcium. The anti-inflammatory effect of the same doses of sodium salicylate and butazolidine was controlled on the extract of hind-paw oedema. The results showed Sandosten-calcium and prednisolone to decrease fluorescein permeability, whereas under the conditions applied salicylate and butazolidine markedly increased the inflow of fluorescein into the aqueous humour.

The results have raised the possibility that non-inflammatory permeability is increased by salicylate and butazolidine.

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Mode of action of certain antiphlogistic agents

Previous experiments have shown that the anaphylactoid oedema in rats is decreased by some cytostatic agents of various chemical structure. Further studies revealed that these drugs reduce the penetration of fluorescein sodium into the aqueous humour of the rat's eye. This indicates that capillary permeability was decreased by cytostatic agents.

In the present series of experiments the antiphlogistic effect of cytostatics has therefore been analysed. The anaphylactoid reaction caused by certain histamine and serotonin-liberators, like egg-white and dextran, was inhibited earlier than the swelling caused by local histamine and serotonin administration. This suggests that, in addition to their permeability reducing effect, the cytostatic drugs inhibit the liberation of certain biogenic amines. Adrenalectomy had no influence on this antiphlogistic activity.

Next, the desensitization to capsaicin and its effects on serotonin sensitivity were studied. Desensitized rats proved less susceptible to the effects of serotonin on diuresis and body temperature. The reduced sensitivity was relative since, after high doses of serotonin, ulcer development and temperature decrease were identical in the desensitized and the control rats.

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Effect of various anti-inflammatory agents on the histaminopexic activity of blood serum

Histamine seems to play a significant role in certain inflammatory changes. Onthe other hand, the *milieu interieur* is able to bind histamine (PARROT and LABORDE 1960) and thus apparently counteracts the histamine effect. Hence, it seemed interesting to examine whether anti-inflammatory agents were capable of restituting the decreased histaminopexy.

The experiments were performed on male rats weighing 80—120 g, the histaminopexic activity of which was suppressed by adrenalectomy and castration. The animals received 0.9 per cent NaCl solution to drink. The anti-inflammatory agents were administered intraperitoneally.

It could be established that the histaminopexic activity of the blood serum reappeared, in fact, under the influence of sodium salicylate, antipyrine, colchicine, phenylbutazone and a thiophene derivative.

The conclusion may be drawn that a peripheral cortisone-like action is involved which does not, however, require the presence of adrenocortical hormones. The effect observed differs from the antihistaminic action, since mepramine exerts merely a slight effect, whereas a phenothiazine compound possessing only anti-inflammatory, but no antihistaminic property, proved 50 times more effective.

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The significance of biogenic amines in inflammation

Using the granuloma-pouch method, we have studied in rats the influence of biogenic amines and bradykinine upon the inflammatory process. We could show that tissue depleted of histamine by the administration of 48/80, and tissue in which histamine liberation was inhibited by treatment with azulene or epsilon-amino caproic acid, respond differently to inflammation than does normal tissue or such with an increased histamine content.

Tissue with low histamine content and/or tissue in which histamine cannot be mobilized display an inflammatory response with less oedema, less necrosis and more healing tendency. Tissue rich in histamine, a condition created by administration of As_2O_3, shows the opposite tendency with stronger inflammation and more hyperaemia. This points to a direct quantitative relationship between histamine content and the intensity of inflammation.

Bradykinine, which also participates in the inflammatory process, had a weaker action when the tissue had been depleted of histamine.

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A permeability factor isolated from lymph node cells and its possible role in delayed hypersensitivity

Extracts of lymph node cells have been found to contain a factor (LPF) which is capable of increasing vascular permeability in the skin of rats. LPF has been differentiated from many other permeability factors by means of antagonists and parallel quantitative assay.

The possible role of LPF as a mediator of the inflammatory changes that occur during delayed hypersensitivity has been discussed.

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Effect of ganglionic blocking agents on the Shwartzman phenomenon

Local quantitative SHWARTZMAN phenomenon was produced in rabbits by administering five preparing doses in decreasing concentration. The phenomenon was induced by E. coli 0111 endotoxin. As ganglionic blocking agents-TEAB and hexamethonium were used, intravenously in doses inhibiting trans mission in the superior cervical ganglion. The provoking dose of endotoxin did not influence ganglionic transmission.

Necrosis and severe haemorrhagic inflammation were found in every control animal. No necrosis was observed in rabbits pretreated with TEAB and also haemorrhagic inflammation was slight. Hexamethonium proved to be a weaker inhibitor than TEAB.

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Glycoprotein concentration of blood and lymph in turpentine-induced inflammation

Inflammation has been induced in 12 dogs weighing 10—12 kg, by injecting 1.5 ml turpentine (Ol. Terebinthae rectif.) subcutaneously in the ear. The concentration of glycoproteins and neuraminic acid was determined in the blood of the saphenous vein prior to the injection. 24—48 hours following the injection of turpentine, lymph and venous blood were taken from the vessels draining the inflamed area and at the same time from the corresponding vessels on the contralateral side, and the concentration of glycoproteins and neuraminic acid was determined.

The protein-bound hexose in the lymph of the inflamed area was found to rise significantly as compared to the control animals 48 hours following the injection of turpentine. The concentration of the neuraminic acid developed differently, namely, the neuraminic acid level was significantly lowered in the samples taken after 24 hours.

Glycoprotein concentration and neuraminic acid level of the venous blood increased parallel with the inflammatory reaction.

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Radioisotope technique for the investigation of certain factors in acute experimental inflammation

The interpretation of tests observing the macromolecules leaving the circulation in the course of acute inflammation are based on the supposition that the intensity of the dye-induced colour, or the number of disintegrations connected with the local accumulation of radioisotope macromolecules, are closely correlated with the basic event of the acute inflammatory response.

We have studied some acute inflammatory changes induced on the rat's hind-paw by testicular extract, thermal injury, or kallikrein, following the intravenous administration of ^{131}I-labelled human or rat serum albumin. The distal part of the paw of unanaesthetized animals, or samples of serum and punctured oedema-fluid were placed in front of the window of a well-type scintillation counter. When total radioactivity was at its peak in the paw, *i.e.* within an hour after the stimulus had been applied, the animals were bled and talocrural exarticulation was performed. The difference between the activities of the treated and untreated paws was regarded as inflammatory activity.

According to our calculations, there was a good correlation

1. between the amount of oedema fluid and the inflammatory activity, and

2. between the relative ^{131}I-albumin concentration and the amount of oedema-fluid.

3. On the other hand, there was no linear correlation between ^{131}I-albumin accumulation and the grade of visible swelling, *i.e.*, a significant inflammatory activity could be present also when visible swelling was inhibited by a systematic anti-inflammatory agent. Total ^{131}I-albumin accumulation consists of different compartments which are able to change, at least in part, independently of one another. Apart from the inflammatory activity of the blood and the oedema fluid, a significant part of the inflammatory activity may reside anywhere in the tissues.

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Certain parameters of acute experimental inflammation before and after inhibition by salicylate or cortisone, investigated by a radioisotope technique

Unlike acute inflammation caused by thermal injury, testicular extract induced oedema of the rat's hind-paw is inhibited by a large dose of sodium salicylate given some hours, or large doses of cortisone administered several days, before the experiment.

On the basis of the correlation between the amount of oedema fluid and its relative ^{131}I-albumin contents, the conclusion has been reached that — if ^{131}I-albumin and fluid go hand in hand — the increase of inflammatory oedema formation is not connected with a simultaneous increase in the concentration of ^{131}I-albumin escaping from the circulation. Functionally, this means that in the course of inflammation the physiological permeability process is not enhanced. In fact a pathological process seems to be involved, which correlates with the intensity of different injuries. Recent electron-microscopic observations (MAJNO and PALADE 1961) seem to agree with these functional data.

According to our results, the inflammatory ^{131}I-albumin activity significantly increases even if inflammatory swelling is inhibited. A considerable part of this activity is not accounted for by the circulating blood or the oedema fluid. Inflammatory irritation may thus induce invisible changes even if visible signs and symptoms caused by the irritant are suppressed. Moreover, this undefined tissue activity is present several hours after the inflammatory swelling has disappeared.

As well known from clinical experience, salicylate and hydrocortisone are suppressing the inflammatory signs and symptoms and yet fail to prevent the subsequent development of tissue damage. We suppose that an ideal anti-inflammatory agent would be one which is able to inhibit this residual tissue change. Our radioisotope technique seems to present an adequate screening test for these agents.

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The starting period of inflammation

The accumulation of fluid, blood protein, and artificial colloid has been studied in the inflammatory process induced by xylene in mice. The increase in weight of the ear treated with xylene was estimated and compared with

the weight of the untreated contralateral ear. From the wet weight difference the accumulation of fluid, from the dry weight difference that of the blood proteins was calculated.

In the first five minutes after xylene treatment there occurred fluid retention which reached 30 per cent of the maximum observed after 25 minutes. In the first five minutes no accumulation of protein was observed; the protein level at 10 minutes was 1 per 100 ml and at 25 minutes, 2.2 per 100 ml.

Artificial colloids displayed a considerable accumulation in the first five minutes whereafter the intensity of their accumulation diminished.

According to the findings, the accumulation of fluid, proteins, and artificial colloid, respectively, are independent processes.

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The mechanism of ^{198}AU colloid accumulation in model inflammation

In inflammation induced by 10μg of histamine, the mechanism of colloid gold accumulation has been studied in rats.

^{198}Au accumulation was found to be the most intensive in the first 15 minutes of inflammation. The phenomenon cannot be explained by the rapid decrease of the isotope's blood level, because, when the colloid gold was administered intravenously 15 minutes after the induction of inflammation, there was only slight accumulation. Accumulation was the less the later the colloid was given after inflammation had been elicited. As evidenced by the findings, a weakening of the activity of the system responsible for accumulation is responsible for the reduction. This system could be reactivated to almost the initial value by a repeated injection of histamine.

This observation allows the conclusion that the mechanism responsible for the fixation of colloid is activated during the induction of inflammation. This activity is rapidly reduced in the course of the inflammatory response, but may be evoked again by repeated administration of histamine.

In further experiments it has been shown that the oedema fluid contains part of the accumulated ^{198}Au.

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Accumulation of fluid and of artificial colloid in inflamed tissue

Inflammation was induced on the rat paw by histamine treatment and the influence of temperature on the accumulation of ^{198}Au colloid and fluid, respectively, was studied by changing the temperature of the bath surrounding the rat's paw.

Colloid accumulation reacted more sensitively to changes of temperature than did the fixation of fluid. When the temperature of the bath was lowered from 30°C to 15°C, colloid accumulation was reduced by 50 per cent, while the reduction of fluid accumulation amounted to 15 per cent only. Further lowering of temperature has been found to exert a more marked influence on the accumulation of fluid than on colloid accumulation. At 0°C the accumulation of fluid practically ceased, while colloid fixation was still 20 per cent of the value obtained at 30°C.

SYMPOSIUM ON THE EARLY MANIFESTATIONS OF CONDITIONING

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Some new developments in the study of conditional reflex processes

A short historical survey has been presented of the two points of view of modern brain research, the extreme analytical and the pure behavioural method. The shortcomings of both aspects have been analysed, emphasizing the need for the elaboration of a new methodology, unifying both points of view.

Some experimental achievements of the last two decades promising new perspectives has been analysed and possibilities to advance a common physiological and information-theoretical approach are suggested.

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Diencephalic, brain-stem and hippocampal drive mechanisms in the organization of learning

Some basic properties of processes similar to natural driving forces elicited by the stimulation of different regions of the hypothalamus, median thalamus and the midbrain reticular formation, have been determined by means of a recently developed "double conditioning" method (simultaneous approach and avoidance conditioning) in cats.

In agreement with a former study it has been evidenced that the effects of stimulations (activation and inhibition of conditional reflexes) are extremely variable and always determined by the actual experimental environment.

In the course of a systematic study, cyclic variations of general excitation and inhibition accompanying and following stimulations have been observed. A comparative analysis of these variations revealed specific functional differences between the driving forces elicited from the hypothalamus, thalamus, and reticular formation.

Some insight into the higher control of the periodic variations has been gained by destroying the hippocampal formation.

The observations offered a new common interpretation of approach and avoidance learning, and at the same time a more physiological explanation of self-stimulation than those available at present.

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Conditioning of evoked potentials: an experimental model of learning

The conditioned evoked potentials obtained by the association of different peripheral visceral and somatic afferent stimuli proved to be a simple model of learning. By this means it is possible to control the parameters of the stimuli as well as the intensity and time relations of the central impulses. Splanchnic, ischiadic, and auditive stimuli were associated in different combinations in unanaesthetized curarized cats. The changes in the evoked responses allowed to conclude to some fundamental characteristics of the learning process.

The *time-relations of the associated stimuli.* By simultaneous application of splanchnic and ischiadic stimuli the amplitude of the weaker splanchnic evoked potential was doubled after reinforcement. If the test-stimulus was followed in 80—500 msec by the reinforcing second stimulus (either in splanchnic — ischiadic, or in ischiadic — splanchnic sequence), after the associations the test stimulus evoked in addition to its own response a marked potential on the place of the reinforcing second stimulus.

Extinction and delayed inhibition. The conditioned evoked inhibition shows extinction curve in the atypical lack of the reinforcing second stimulus. This process can be inhibited and thus both the extinction and the disinhibition phenomenon are demonstrable electrophysiologically.

After delayed reinforcement (from 80 to 500 msec) the conditioned response appeared with the same delay as the former reinforcing stimulus. This means that the learned nature of the delayed inhibition cannot be proved.

Intensity relations. In the case of delayed reinforcement, if the test stimulus is weak and the reinforcing stimulus strong, or *vice versa*, the test stimulus alone elicits two conditioned responses *viz.* one on the place of the weak stimulus, the other on the place of the reinforcing one. Thus the pavlovian "law of stimulus-intensity" cannot be demonstrated electrophysiologically.

Topographical relations. If stimuli with divergent cortical representations are associated (*e.g.* splanchnic or ischiadic stimulus with auditive one), the learned response appears on both projection-areas.

On the base of the model-experiments, the mechanism of elementary learning processes has been discussed, especially concerning the possible role played by the post-tetanic potentiation phenomenon.

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Conditioning in reticular units

Paper not submitted.

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Investigations concerning the construction of the visceral cortex

In recent years more and more material has accumulated concerning the analysis of interoceptive informations in the central nervous system. The author has proved that after total decortication no interoceptive conditioned reflex can be developed even with 200 associations. Histological control showed extensive destruction in the central nervous system. Reflexes can be developed after unilateral decortication. Bilateral destruction of the sigmoid gyrus suspended the viscero-mechanical and viscero-chemical reflexes for 2—7 months and caused degeneration in certain thalamic nuclei. During EEG registration, on viscero-chemical stimulation changes of similar character occurred in the motor cortex as well as in the frontal and hinder limbic areas. The connection of the limbic cortex with the 6, 4; and to a similar extent with the 1, 2, 3, 7, 19 areas was demonstrated with the fibre degeneration method.

According to these data, the author approves of the use of the term "visceral cortex".

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The role of basal forebrain structures in the avoiding conditioned reflex activity in rats

The role of diencephalic and striopallidal structures in the integration of avoiding conditioned reflex activity has been studied. The animals were trained to jump at the shelf on the sound stimulus associated with painful electric shock. Electrolytic lesions placed in the basal septal area, strio-pallidal system and medial forebrain bundle blocked completely the avoiding conditioned reflex activity. Other lesions placed in the rostral septum, caudate

nucleus and amygdaloid complex of nuclei failed to influence the conditioned reflex performance. The neuroanatomical structures whose lesions impaired the conditioned reflex activity, participate in the meso-diencephalic activating mechanism which plays a decisive role in the integration of behavioural and EEG arousal reaction, as well as in the maintenance of motivative driving force related to the conditioned reflex activity.

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The role of motivation in conditioning: its neural and humoral factors

The functional and neuroanatomical characteristics of the behavioural and EEG arousal reaction, habituation, and the somato-motor manifestations of "drive" playing a role in the establishment of temporary connections have been examined. Observations in waking cats showed that the disruption of the mesodiencephalic circuit (mesencephalic reticular formation → thalamic intralaminar nuclei → strio-pallidal connections → basal septal area → medial forebrain bundle) abolishes the behavioural and EEG arousal reactions to environmental stimuli and blocks previously established conditioned reflexes as well as self-preservating processes. The limbic structures through ample connections can activate and inhibit the activity of the meso-diencephalic activating mechanism. Electrical stimulation of the basal septal area enhances the habituation of novel stimulus and increases the discriminative activity in conditioned reflex situations. Both processes form essential parts of the internal inhibitory brain mechanisms and play important roles in the decoding of environmental signals.

The somatomotor manifestations of "driving force" concerning the early signs of learning processes may be characterized by the spontaneous goal-directed motor activity (intersignal reactions) in the course of conditioning. The intertrial spontaneous goal-directed motor activity corresponds to the first event in the establishment of temporary connections. The neural and humoral factors playing a role in the development of spontaneous goal-directed motor activity during the conditioning and their importance in the formation of temporary connections has been discussed.

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Elementary temporary connection in midbrain-animals

After complete transection at the level of the colliculus superior (high decerebration) in cats, the possibility of a temporary connection has been examined for several days. The apnoe induced by stimulation of the central end of the vagus nerve was conditioned with the stimulation of the pelvic nerve. Before the associations pelvic stimulation changed neither the amplitude nor the frequency of breathing movements. After 60—100 associations, pelvic stimulation — without vagal reinforcement — caused respiratory amplitude and frequency to diminish or lead to complete apnoe. After 200—300 associations, this reaction became constant and persisted for 24 hours. The phenomenon may be regarded as an elementary temporary connection at midbrain level.

GERBNER, M. and PÁSZTOR, E.
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The role of the frontal lobe in conditioned reflex activity

Destruction of different parts of the premotor cortex altered the conditioned reflex activity of dogs. Destruction of the gyrus proreus caused the disinhibition of the inhibitory processes. Resection of the inferior part of the sigmoid gyrus was followed by a decrease of the positive conditioned reaction. The conditioned reflexes elicited by light stimuli suffered more damage than those elicited by sound stimuli. The role of certain frontal areas in positive and negative conditioning has been discussed.

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The role of the frontal lobe in food-acquiring behaviour in the dog

(With film demonstration)

Destruction of the inferior part of the sigmoid gyrus renders the dogs incapable of carrying out the previously learned motor reaction of food-acquiring through a grating.

SEDLAČEK J.
INSTITUTE OF PHYSIOLOGY, CHARLES UNIVERSITY, PRAGUE, CZECHOSLOVAKIA

Ontogenetic development of temporary connection

Paper not submitted.

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Changes in the EEG and evoked potentials during avoidance conditioning in rats

Paper not submitted.

HECHT, K.
INSTITUTE OF CORTICO-VISCERAL PATHOLOGY, BERLIN, GDR

Mechanism of avoidance conditioning in the rat

Paper not submitted.

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Electrophysiological studies of the hippocampus in man

The diagnostic and therapeutic use of electrodes implanted in the hippocampus, amygdala and related structures in cases of temporal lobe epilepsy has afforded the opportunity to study the electrical properties of these deep structures in man.

By use of computer analyses it has been possible to trace the electrophysiological connections of the hippocampus with other deep centers in the brain and to relate its activity to some facets of memory function.

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PHYSIOLOGICAL INSTITUTE, UNIVERSITY MEDICAL SCHOOL, BUDAPEST AND MATHEMATICAL RESEARCH INSTITUTE, HUNGARIAN ACADEMY OF SCIENCES, BUDAPEST

Mathematical analysis of the EEG of neurotic rats

In 25 white male rats chronic subdural electrodes were implanted. Control EEG records were made under nonstimulus standard circumstances. Then a neurotic state was induced by conflicting unconditioned drinking and electrical

defensive reflexes. Comparing the control records with these obtained after the conflict situation, in the latter beta-like activity was more expressed and, on the other hand, spikes and a frequent variation of synchronized and desynchronized periods occurred. Statistical evaluations showed the following conclusions.

1. BRAZIER's autocorrelation method (manually performed this time) showed in both the normal and the neurotic state weak theta-like activity. After the interference it was the basic direction of the curve that changed.

2. Analyses of the records by the method of SATO and others revealed a decrease of amplitude and a slight increase in frequency patterns was obvious.

3. Background activity (containing no periodic components) was examined by the so-called dynamic averages. In the neurotic state slow waves with high amplitude appeared.

4. The total amount of electrogenesis estimated according to DROHOCKI showed a great variability of the index.

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The role of the hippocampus in paradoxal sleep

Paper not submitted.

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Effect of hippocampal lesions on the learning process

In an earlier series of experiments it has been shown that bilateral hippocampal lesions had no essential effect on simple alimentary or avoidance conditional reflexes, elaborated either before or after the lesions had been inflicted. The only disturbance observed was a hyperactive orientation to the conditional signal.

In a multiple choice delayed conditional reflex situation normal cats could easily achieve criterion at 60 sec delay. Animals with previous hippocampal lesions failed to perform the task even at 10 sec delay. These findings suggested that the hippocampus plays an essential role in processes responsible for recent memory.

In a new series of experiments it has, however, been found, that a well-established delayed conditional reflex could not be destroyed by bilateral hippocampal lesion.

On the basis of a systematic analysis of movement patterns, the conclusion has been reached that the role of the hippocampus must be sought in a comparison and selection of afferent signals and their attachement to appropriate movement patterns.

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Reticular control of splanchnic afferentation

The reticular control of specific afferent impulses of the splanchnic and ischiadic nerves has been studied in unanaesthetized cats. The activity level of the brain-stem reticular formation was established in such a way that the period of stimulation changed between 200 and 5000 msec. The increase in non-specific afferentation thus induced diminished the amplitudes of the evoked cortical potentials of exteroceptive and interoceptive origin in a different measure. Depending on the stimulation time of the reticular formation, the surface-positive phase of the evoked potentials of interoceptive origin was mostly inhibited. The surface-negative wave was slightly facilitated after initial inhibition.

It has been concluded that non-specific activation causes the lower cortical layers to be gradually inhibited, whereas the upper layers go over from inhibition into the state of facilitation. Analysing the periods of certain phases of evoked potentials suggested that the increase of non-specific impulsation decreased the number of neurons responsible for the production of evoked potentials.

ÁNGYÁN, L.
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Some electrical correlates of drive processes elicited from midline thalamic structures

The role of midline thalamic structures in the conditioning process has been studied with the help of the recruiting potential in three different ways.

1. Recruiting responses were elicited in two psychologically opposite situations of avoidance conditioning in order to evaluate the influence of different environmental factors on the potential mechanism.

2. Low frequency stimulation of the n. centrum medianum, the n. reuniens and n. ventralis anterior was used as a conditional signal and the variations of the morphology of the potentials accompanying the development of conditioning was analysed.

3. Stimulations were applied to activate a preestablished avoidance or approach conditional reaction, and the potential configurations by which activation had been elicited were compared with potential configurations not reaching the threshold of activation.

The observations suggested the different parts of the thalamic diffuse projection system to represent — in spite of their common characteristics — different mechanisms. A double functional representation of the region of the centrum medianum and its possible role in the conditional process has been discussed.

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Desynchronizing and synchronizing electrical reactions induced by stimulating dorsal and ventral levels of the amygdaloid complex

Previously it has been shown that fast repetitive stimulation of the amygdaloid complex elicits a low voltage fast cortical activity, similar to the arousal reaction induced by stimulating the brain stem reticular formation.

In the present study it has been observed that within the basolateral amygdala there are two antagonistic systems, one of which desynchronizes while the other synchronizes, the background activity of the neocortex. Experiments were carried out on *encéphale isolé* and *cerveau isolé* cats.

1. Fast repetitive (100—200/sec) stimulation at liminal intensities of dorsal amygdaloid levels (D-3, in particular the central lateral nucleus, A. c. l.) elicits an accelerating-desynchronizing reaction of neocortical electrical activity, mostly recorded from ectosylvian areas. Simultaneously with this cortical response, ample slow and rhythmic waves are generally recorded from the dorsomedian thalamic nucleus. Contrary to the reticulo-cortical desynchronizing effect, which is tonic in type, the response to stimulation of the dorsal amygdala is phasic in nature. The cortical arousal reaction induced by stimulating the dorsal amygdaloid levels persists following complete mid-brain transection *(cerveau isolé* preparation).

2. Fast repetitive stimulation of ventral amygdaloid levels (D-6 to -7, in particular the small-celled basal nucleus, A.b.p.) results in a synchronization of neocortical electrical activity in the form of spindles and slow waves. The synchronized responses are more evident in those areas where a desynchronized activity was present prior to stimulation. The synchronizing reaction is not dependent on synchronizing structures from the lower brain stem, since it persists in the *cerveau isolé* preparation.

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Remanence phenomena in the cat's cortical sensory areas

The following variants of remanence phenomena in the auditory and visual cortex have been observed in *encéphale isolé* cats.

1. After protracted acoustic stimulation (0.5—3/sec clicks), spontaneous potentials with no direct connection with an acoustic stimulus appear in various areas of the auditory cortex, exhibiting a morphology identical to that of potentials previously evoked by clicks. This phenomenon of remanence mainly occurs in animals with excessive reactivity, displaying numerous spontaneous arousal reactions and prolonged after-effects following electrical stimulation of the unspecific activating system.

2. After protracted stimulation with rhythmic clicks, fast repetitive stimulation of the reticular formation induces certain potentials independent of any acoustic message and identical to those elicited by clicks in previous stages of the experiment. These potentials elicited by reticular stimulation generally reproduce the rate of clicks currently used during the experiment.

3. After protracted stimulation by rhythmic shocks (1—3/sec) of the lateral geniculate body, spontaneous potentials independent of any geniculate shock are recorded from the visual cortex, reproducing the morphology of geniculo-striate responses, especially of positive-negative waves. These spontaneous potentials develop into a seizure-like pattern. The spontaneous response occurring in the visual area after protracted rhythmic stimulation of the lateral geniculate body persists after extensive isolation of the striate area.

The mechanism of the remanence phenomenon and the role of the reticular formation in evoking spontaneous potentials (reproducing the evoked responses of previous stages) have been discussed.

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Negative potentials of the cortical surface

According to data in the literature, negative potentials of the cortical surface mean the impulse of the dendrites of the I. and II. layers. Direct cortical stimulation plays a considerable role in the investigation of the physiological importance of these potentials. A single short (0.05 msec) electrical stimulus in deep pentobarbital anaesthesia causes a negativity lasting 20—30 msec. The amplitude of the negative wave changes with the intensity of the stimulus. The application of 1 per cent of gamma-amino-butyric acid (GABA) leads to the reversal of the potential. This is caused by the specific inhibiting effect

of GABA on the depolarizing synapses. Thermocoagulation of the surface layers leads also to the reversal of the potential. The reversal probably means in both cases an excitation of the deeper cortical layers. After a double stimulus the answer to the second takes less than 20 msec. Strychnine had no influence on the effect. The negativity occurring on the second stimulus lasts longer than 600 msec.

According to the results and the data of others, the negativity of the cortical surface is in close relation with the process of cortical inhibition.

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Excitability and projections of sensory pathways to the hypothalamus

Paper not submitted.

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Presynaptic inhibition in the central nervous system

Paper not submitted.

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Vegetative and EEG responses elaborated to the effect of hypoxia

In different animal species the conditioned vegetative and EEG responses elaborated to indifferent (optic + acoustic) stimuli coupled with inhalation of air with 6 to 10 per cent oxygen have been studied by recording oxygen-consumption, body temperature, respiration, and electrical activity of the neocortex and of different subcortical structures. The early signs of the vegetative conditioned response and the bioelectrical manifestations associated with it have been analysed.

The vegetative responses were found to be identical with or reciprocal to the effect of the unconditioned, hypoxic, stimulus. The EEG patterns indicated the conditioned character of both types of vegetative response.

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Central nervous mechanism in the adaptation to the body temperature-lowering effect of histamine

According to data in the literature, lowering of body-temperature in response to histamine is progressively diminishing and after the 3rd—4th dose the drug has no such effect. At the same time the similar activity of other substances persists unchanged.

An enhanced elimination of histamine, as a possible explanation of this "tachyphylactic" phenomenon, could not been verified experimentally (histaminase, antihistaminase determination).

Studying in rats the body-temperature-lowering effect of repeated subcutaneous injections of histamine it has been found that saline injected after the third, almost ineffective histamine dose suspended the adaptation to histamine; subsequent administration of histamine again caused a marked lowering of body-temperature.

The phenomenon points to the role of the central nervous system in the development of rapid adaptation to histamine which may involve a mechanism similar to habituation or conditioned reflexes.

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Influence of pituitary-adrenocortical function on avoiding conditioned reflex activity in the rat

The influence of short-term ACTH administration and adrenalectomy on avoiding conditioned reflex activity was investigated in rats. A significant increase of reflex performance accompanied with a marked decrease of spontaneous goal-directed intersignal motor activity could be observed following a single dose of 2 U/100 g body weight of ACTH. Adrenalectomy failed to influence the conditioned reflex performance, but increased the spontaneous intersignal motor activity.

The findings suggest the role of pituitary-adrenocortical function in the enhancement of internal inhibitory processes during conditioning. The increase in internal inhibition manifests itself by a decrease of spontaneous intersignal motor activity and corresponds to decreased motivation.

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Effects of the mesencephalic reticular formation on some vegetative reflexes

The effect of electrical stimulation of the mesencephalic reticular formation on some sympathetic and parasympathetic vegetative reflexes has been studied in acute experiments in cats and dogs under intravenous chloralose anaesthesia, in certain cases with d-tubocurarine or Flaxedil.

In a first series of experiments in 15 cats and 5 dogs the effect of liminar and supraliminar stimulation of the mesencephalic reticular formation, by means of monophasic rectangular currents, was studied on the carotid sinus pressor reflex induced by bilateral occlusion of the common carotid for 15—20 sec. Reticular stimulation was performed using stereotaxically implanted silver bipolar electrodes 0.2—0.4 mm in diameter. Histologic examination showed most of the stimulated points were in the midbrain pontile oral reticular nucleus.

In most instances, liminar and supraliminar stimulation of the mesencephalic reticular formation, together with bilateral occlusion of the common carotids, resulted in an increase of the carotid sinus pressor reflex. In rare cases, liminar stimulation of the mesencephalic reticular formation had no effect or diminished the amplitude of the carotid sinus pressor reflex.

In a second series of experiments carried out in 25 dogs, the effect of liminar and supraliminar electrical stimulation of the mesencephalic reticular formation was investigated on the vesico-constrictor reflex induced by stimulation with monophasic rectangular pulses of the central end of the transected pelvic nerve. Bladder contractions were recorded on a kymograph by means of a hydroaeric system; blood pressure was recorded in the right femoral artery. In the course of the experiments two dogs were decerebrated by brainstem transection rostral to the anterior colliculi.

A total of 37 points was explored in the midbrain reticular formation. In 32 cases stimulation of the mesencephalic reticular formation elicited inhibition or occlusion of the vesico-constrictor reflex induced by stimulation of the central end of the pelvic nerve. This effect of the reticular formation persisted after decerebration. In 5 cases, the mesencephalic reticular formation facilitated the vesico-constrictor reflex. Reticular stimulation occasionally influenced the vesical and tensional components of the pelvic reflex in a different manner. Following concomitant stimulation of the mesencephalic reticular formation and of the central end of the pelvic nerve, phasic long-lasting changes (increase or decrease) of the excitability of the vesico-constrictor reflex arch occurred.

A comparison of the two series of experiments shows that stimulation of the mesencephalic reticular formation mostly facilitates the carotid sinus pressor reflex and inhibits the vesico-constrictor pelvic reflex.

The functional significance of this finding has been discussed.

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Nervous system effects of the components of a cardiopathogenic diet

The cardiopathogenic diet S_{65} has been shown to induce severe functional lesions in the central nervous system even before infarctoid symptoms had appeared. In the present experiments the changes induced separately by each component of the complex diet rich in fat and salts has been studied. Functional central nervous system changes were examined in chronic EEG and conditioned reflex experiments.

A diet with only salt overload brought about practically no change in spontaneous and stimulation-induced electric activity. In the conditioned reflex experiments, only slight and late alterations were demonstrable.

On a diet with only fat overload, the spontaneous EEG showed enhanced frequency with a decrease of amplitudes. Electrical stimulation caused a lengthening of desynchronization time. These changes were more moderate than those induced by the full diet. The number of conditioned responses diminished more than in the case of the diet with salt overload, but less than on the complete cardiopathogenic diet.

The central nervous effects of the cardio-pathogenic diet are thus induced by the single components in a complex way, each component by itself bringing about only minor changes.

SHORT COMMUNICATIONS

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Pulmonary vein reflex and circulatory stabilization

The haemodynamical changes furnishing the basis of the reflex stabilization of blood pressure have been studied in dogs and rabbits. It has been found that on evoking the reflex by an inflatable balloon introduced into the pulmonary vein, simultaneously with the lasting fall of blood pressure, the cardiac output measured by the isotope dilution method decreases by 50 to 80 per cent, and peripheral resistance increases. As the cardiac output may decrease without a change in blood pressure, it has been concluded that the primary effect is the one exerted on the cardiac output. The stabilizer reflexes are characterized by their action on the arterio-venous shunts. The increase in the pulmonary shunt circulation is indicated by the fall in arterial O_2 saturation. Since radio-circulographic studies showed an increase of pulmonary circulation time, and the decrease of arterial O_2 saturation could be eliminated by the inhalation of pure oxygen, it has been concluded that shunting is taking place in the capillary area. The isotope dilution curve obtained in the bronchial veins (^{131}I albumin) indicated a simultaneous opening up of the pulmonary-bronchial shunts. At the same time the broncho-pulmonary shunts normally open are closed, as shown by the isotope dilution curve gained from the left atrium following the intraventricular administration of the isotope. All this means a complete redistribution of the pulmonary circulation.

Using SAPIRSTEIN's method, a significant redistribution of the cardiac output fractions has been shown to occur in rabbits during reflex stabilization. The liver, kidney, lung and cardiac fractions decrease, while the muscle fraction increases significantly. This allows the conclusion that in the reflex hypotensive stabilization of blood pressure a marked redistribution of cardiac output fractions forms the basis of the new circulatory equilibrium.

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Extrinsic and intrinsic reflex mechanisms of pulmonary veins

In dogs under morphine-chloralose narcosis stimulation of the terminal part of the pulmonary veins evokes a long-lasting depressor reflex stabilizer in nature, resembling the coronary sinus reflex described earlier. Stimulation

was effected either mechanically by means of an inflatable balloon or by surface application of diluted (0.1%) veratrine solution. This reflex, too, is characterized by its "all or nothing" nature, by its trigger-like action and by the decrease of the arterial O_2 saturation. The latter effect is diminished by thoracal sympathectomy. Stimulation of the receptors of the pulmonary veins causes a reduction of the arterial O_2 saturation and a slight fall in blood pressure even after previous transection of the vagal afferents of the reflex. It is probably through axon reflexes or propagative smooth muscle reactions that the latter intrinsic mechanism might play a role in the stabilization of the effects of the v. pulmonalis reflex, because the reflex responses elicited for a short time can be abolished by vagotomy, whereas, if the receptors are stimulated for longer periods, the responses are irreversible even after vagotomy. In the reflex reaction the single elements of the pulmonary vascular bed play a complex role. From the fact that in the case of a stabilized reaction the existing state is enhanced by vasodilators and vasoconstrictors alike, it is concluded that a total redistribution of pulmonary circulation, with constriction of some vascular areas and dilatation of others, occurs at the same time. In that state the dilated vascular beds are capable of further dilatation only, and the constricted vascular beds only of further constriction.

DEBRECZENI, L., SZENTIVÁNYI, M., ÓVÁRY, I. and JUHÁSZ-NAGY, A.
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Hypothalamic control of coronary vasomotor tone

In earlier experiments the peripheral sympathetic innervation of the coronary blood vessels has been clarified. In the present study the diencephalic vasomotor control of the coronaries has been investigated. Mongrel dogs under morphine-chloralose anaesthesia were used. Coronary blood flow was measured by a rotameter or thermoprobes. The hypothalamus was stimulated monopolarly with needle electrodes placed by means of a stereotaxic apparatus. Electrode localization was checked histologically after the experiments. It was found that precisely localizable coronary vasomotor reactions could be evoked by stimulating different hypothalamic areas. These reactions often set in independently of the blood pressure responses.

The medial groups of the posterior hypothalamic nuclei mainly represent coronary constrictor, the ventro-lateral and cranial groups mixed cardiomotor and coronary vasomotor structures. From the areas of the anterior and medial diencephalic gray matter near the cerebral base, cholinergic coronary dilator effects could be evoked. On stimulation of the areas near the pituitary body the afore-mentioned effects appeared together with "tonic" coronary constrictor responses, elicited presumably by vasopressin mobilization.

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Coronary circulation of the avian heart

It was shown earlier that the metabolic adaptation of the mammalian coronary blood vessels depended on their vasomotor tone. In the present study coronary vasomotor control and coronary metabolic adaptation has been investigated in animal species displaying a high basal level of cardiac metabolism. Chicken and pigeon hearts isolated or *in situ*, perfused by LANGENDORFF's method, were used. In addition to coronary flow cardiac O_2 consumption was measured continuously by means of a densitometer. The degree of metabolic adaptation of the coronaries was determined by the hypoxia test. It was found that the high rate of coronary flow in avian hearts as compared with mammalian hearts was accompanied by an excessive adrenergic coronary constrictor tone. This constrictor tone was associated with a much higher degree of metabolic adaptation than in the case of mammalian coronaries.

The ability of avian coronaries to react to metabolic stimuli could not be blocked either by repeated hypoxia or by drugs, *i.e.* these vessels are greatly ensured against coronary "rigidity" analogous to human angina pectoris. This agrees well with the observation that the posterior pituitary extracts relieving the "rigidity" of the mammalian coronaries evoke a marked adaptative increase of coronary flow in the avian heart.

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Investigations into the dermato-cardiac reflex

In ischaemic heart disease the sensory impulses are known to irradiate from the heart to the skin areas of the Th_{2-7} segments. In cat experiments it has now been studied whether daily painting with a skin irritant of the defurred left side of the cat's chest would produce changes in the ECG and myocardiac morphology.

Of the 22 experimental animals 9 died after 2 to 3 weeks of treatment, the others were killed between 24 and 30 days. Every animal but two showed ECG changes, mostly an inversion of T in lead II or III and partial atrio-ventricular block. Sinus bradycardia and lability of T in lead I were frequent. Even serious changes (complete atrio-ventricular block, deep Q, bundle branch block) regressed within a few days.

The ECG signs appeared after 3 to 5 days of treatment in 9 animals, after 6 to 10 days in 6 and after 11 days in 5 animals. We examined the effect on the ECG of painting the skin with weak and strong irritants. In the severest cases marked venous hyperaemia and necroses occurred in the myocardium.

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Ultrastructure and some physiological properties of the embryonic heart

Hearts from rat embryos and newborn rats from the 10th day of the conception till the 20th day of extra-uterine life were examined electron-microscopically and light-microscopically. In the earliest period the mesenchymal cells develop into myoblasts in the ventricles, and it is there that the first cardiac contractions appear. The myocardial cells mature and multiply faster in the ventricles than in the atria, whereas the atria show a greater tendency to spontaneous impulsation and spontaneous rhythmic activity than the ventricles, even before the conductive system has developed. The ultrastructure of the myocardial area performing the pacemaker function is in many respects similar to the conductive system of the adult animal. The ventricular and auricular working muscle fibres differ from each other in the embryo and to some extent in the adult animal, and these differences can be explained by developmental and functional factors. The rat heart continues to mature after birth, the embryonic characters are lost only when the eyes of the newborn animal open up or when the voluntary muscles become active, by the end of the second week.

GYÉVAI, ANGELA and CSAPÓ, I.
DEPARTMENT OF MORPHOLOGY, INSTITUTE OF EXPERIMENTAL MEDICAL RESEARCH, HUNGARIAN ACADEMY OF SCIENCES, BUDAPEST AND INSTITUTE OF HISTOLOGY AND EMBRYOLOGY, UNIVERSITY MEDICAL SCHOOL, BUDAPEST

Behaviour in vitro of the dissociated myocardiac cells of the chick embryo

(A motion picture)

Cultures of the isolated cells of the embryonic heart are suitable media for studies of the effects of certain drugs active on the heart and also for the resolution of many histophysiological problems connected with cardiac development. The take and behaviour of trypsinized embryonic chick heart cells were recorded cinematographically. About 24 hours after explantation the adherent and elongated cells began to pulsate, with a difference in frequency between the atrial and ventricular cells. Treatment with 1μg/ml of strophanthin (SCHWACH) caused an increase of frequency and arrhytmia in a large percentage of the cells. Likewise, the transfer of impulses from cell to cell was impaired.

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Effect of Phlogodym on the blood fibrinogen level in traumatic shock

According to our investigations in the mechanism of NOBLE-COLLIP drum shock in the rat, the formation of a fibrin film on the internal surface of the capillaries may play a role in the increase of capillary permeability. It has namely been shown that after the induction of shock in addition to thrombin inactivation, the fibrinogen level decreases, because the fibrinogen is utilized for the capillary fibrin film formation. It has been attempted to prevent the development of traumatic shock by the use of Phlogodym, a neodymium pyrocatechol disulphonic acid complex, synthetized by JANCSÓ and found by him to decrease capillary permeability and blood clotting. Contrary to expectation, the intravenous injection of Phlogodym greatly increased the severity of traumatic shock and caused a dramatic drop to nearly zero in the blood fibrinogen level, as confirmed by immunological tests. The fall of the fibrinogen level was not due to an increased fibrinolysis, because EACA did not inhibit it, whereas heparin, which enhances fibrinolysis, inhibited it. The results shed light also on an as yet unknown phenomenon, on the possibility of a "Phlogodym-heparin" antagonism. This phenomenon is under nvestigation.

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Studies on the effect of a water-soluble corticosteroid analogue in experimental haemorrhagic shock

Standardized haemorrhagic shock was induced in 90 dogs by a "reservoir technique" developed by the present authors. The maximal bleeding volume amounted to about 48 per cent of the circulating blood volume. The effect of a new steroid derivative (11 beta—17 alpha-dihydroxy-3-20 dioxo-21-N(N'-methyl- piperazinyl)-1,4-pregnadien HCL, Richter, Budapest) on the circulatory and metabolic changes of shock and on survival rate has been studied. Under the conditions employed the steroid had no influence on the bleeding volume. In doses of 15 mg/kg the steroid significantly increased the blood pressure of the oligaemic animals, improved the survival rate and diminished certain metabolic changes caused by shock. To elucidate the mode of action, the effects of the steroid on circulating plasma and red cell volumes as

well as on the vascular system proper were studied in normal dogs and in dogs in shock.

It has been observed that by the administration of the steroid while the shock is developing the irreversibility of haemorrhagic shock may be delayed.

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Regulation of hepatic circulation

In previous investigations it was found that in shock, when portal circulation is diminished, hepatic arterial blood flow remains unchanged or increases. To study this phenomenon, in 13 dogs a shunt was created between the portal and the femoral vein, and a rotameter was ligated into the hepatic artery. In 47 experiments, whenever the portal blood was diverted from the liver and conducted toward the periphery, hepatic arterial flow increased, sometimes to double the initial rate. In contrast, following occlusion of the hepatic artery, portal flow did not change in the 5 cases examined.

It has been attempted to elucidate the mechanism of the dilatation of the hepatic artery. Injected directly into the artery, both adrenaline and acetylcholine increased the rate of flow and decreased the resistance. The increase in the rate of flow caused by the shunt could not be prevented either with dibenzylamine or with atropine. Procaine injected directly into the artery was likewise ineffective.

SOLTI, F., ISKUM, M., SOMLYAI, L. and NAGY, J.
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Effect of papaverine on extremital circulation in dogs with isolated perfused extremital circulation

The effect of papaverine on extremital circulation has been studied in dogs of which one limb was isolated from the systemic circulation and perfused by means of a HUFNAGEL heart pump. Extremital blood flow was determined by means of rotameters ligated into the femoral artery and by measuring the venous outflow from the isolated limb. In response to the administration of 0.08 g papaverine, blood flow significantly increased in the isolated limb, in spite of a fall in blood pressure in the lower limb. The increase of blood flow and the decrease of vascular resistance lasted for more than half an hour. Papaverine injected into the systemic circulation caused a fall of blood pressure, a slight decrease of extremital blood flow and a slight decrease of extremital vascular resistance.

ISKUM, M., SOLTI, F., PÉTER, Á., RÉV. J., FÖLDESY, K. and HERMANN, R.
FIRST DEPARTMENT OF MEDICINE AND DEPARTMENT OF NEUROLOGY, UNIVERSITY MEDICAL SCHOOL, BUDAPEST

The effect of alcohol infusion on cerebral bloodflow and metabolism

In 12 patients with normal circulation, the effects of 200 ml of 10 per cent alcohol on cerebral blood flow, cerebral venous pressure, cerebral oxygen consumption, and cerebral potassium and glucose uptake has been studied. Cerebral blood flow was determined by the N_2O method, cardiac output was estimated on the basis of the dye dilution principle, using EVANS blue. The infusion of alcohol has been found to increase cardiac output and slightly to increase cerebral blood flow. Blood pressure usually showed a minor rise, the calculated cerebral vascular resistance did not change significantly. Cerebral oxygen uptake, potassium and glucose uptake increased.

CSALAY, L. and TÓTH, T.
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Humoral factors in the mechanism of experimental neurogenic hypertension

In previous experiments, the mechanism of neurogenic hypertension induced by repeated presentation of light, sound and electrical stimuli was investigated. The EEG showed increased excitation in the central nervous system and an increase of the corticosterone level in adrenal venous blood. The EEG changes (acceleration of frequency, decrease of amplitude) appeared soon, before the blood pressure had risen, while adrenal hyperactivity appeared only after hypertension had developed. In hypertension induced by a similar method HÄNDEL *et al.* found organic renal lesions.

In the present experiments it has been investigated whether the neurogenic hypertension could be transferred humorally to normotensive rats. To elucidate this, capillary circulatory connections were created between the rats with neurogenic hypertension and normotensive rats.

It was found that in normotensive rats sutured to hypertensive animals blood pressure increased after the capillary connection had been established. Parabiosis of two normotensive rats caused no increase in blood pressure. The importance of humoral factors has been emphasized.

GÁTI, T., RIGÓ, J., GYENGE, K. and SÓS, J.
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Changes of the cold pressor reflex in rats fed a cardiopathogenic diet

The cardiopathogenic diet causes in rats an elevation of blood pressure during the second week and hypertension during the third week of feeding. In rats which succumb as a result of an infarctoid cardiac change during the 6th to 8th week, the vascular changes are demonstrable histologically. In the present experiments, the cold pressor test was used for examining vascular wall function. The animals were placed for 30 minutes in a refrigerator of 4°C temperature and their blood pressure was measured continuously. On the fourth day the rats fed the cardiopathogenic diet showed a more marked and more lasting rise of blood pressure than the controls. After six weeks diet the hypertensive vascular reaction reached three to four times the control value. The increase in sensitivity to the pressor effect was correlated with changes in the ion content of the vascular wall. By the administration of magnesium, the increase of sensitivity can be modified to an extent depending on the dose, and the hypertensive vascular reaction may even be turned into a hypotensive one.

RIGÓ, J., GÁTI, T., PÓSCH, E. and SÓS, J.
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Changes in the electrolyte content of the myocardium following coronary ligation in the dog

In previous experiments the myocardial K and Mg concentrations were found to decrease in rats, cocks and dogs fed a cardiopathogenic diet. NICKERSON *et al.* ascribed the development of infarctoid cardiac changes to an intracellular K deficiency, while RUISSEAU and MORI regard the Mg deficiency as the primary factor. According to MEY, in human hearts with infarct, or around the infarct the K content is decreased.

In our present studies the myocardial electrolyte contents have been investigated in dogs, following ligation of the descending ramus of the left coronary artery. Six dogs were used. Four days after ligation the dogs were exsanguinated and muscle slices were cut from the normal and infarcerated parts of the heart for Na, K, Ca and Mg estimation.

The ECG and histological studies proved that infarction had developed. The chemical tests showed in the area of the infarction decreased K and Mg contents, the latter from 18.7 mg to 14.2 mg per 100 g. At the same time,

in the infarction area the Na concentration increased from 127 mg to 186 mg per 100 g and the Ca concentration from 20 mg to 27 mg per 100 g. The electrolyte concentration in the adjacent and apparently normal areas were between the normal and those obtained for the area of infarction.

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Serum lipoproteins in alimentary cardiopathy

The normal cock serum contains 64.2 per cent albumin + alpha-1 lipoprotein, 26.5 per cent beta fraction, with a ratio between the two of 2.42. In cocks fed a cardiopathogenic diet the corresponding values were 31.1 per cent, 55.4 per cent and 0.55. The cardiopathogenic diet significantly increased the chylomicron fraction. No increase occurred in the alpha-2 lipoprotein value.

In the rat the increase of the beta lipoprotein fraction was observed in 60 per cent of the cases only. In such animals a characteristic feature is the appearance of the normally not visible pre-beta fraction between the alpha-2 and beta fractions. The lipoprotein changes are partly or totally prevented by the addition of oleic and linolenic acid to the diet, whereas the administration of thiouracil greatly increased them. The diet did not cause lipoprotein changes when the Mg content was increased fivefold.

No unequivocal correlation could be demonstrated between the lipoprotein pattern and the histological changes.

SZEKERES, L. and PAPP, GY.
INSTITUTE OF PHARMACOLOGY, UNIVERSITY MEDICAL SCHOOL, PÉCS

The influence of the autonomic nervous system on the mammalian heart's tendency to fibrillation

It was shown a few years ago that the increased tendency to fibrillation of the mammalian heart in hypothermia or hypoxia was primarily due to an increased excitatory state of the autonomic nervous centers regulating cardiac activity. In the study the effects of O_2 deficiency, elimination of vagal or sympathetic tone, stimulation of cardiac nerves and injection of mediator substances on atrial and ventricular fibrillation thresholds have been investigated by recording the changes in rhythmicity, excitability, refractory periods and conductivity.

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The effect of changes in blood pressure and myocardial stretch on tendency to fibrillation

In cats under general anaesthesia, changing the blood pressure from 60 to 200 mmHg had no influence on susceptibility to fibrillation of the auricles and ventricles of the heart *in situ*. Increasing local strain has been developed between two points of the myocardium which had to exceed 120—150 g in order to give a slight increase in the tendency to fibrillation. In contrast to this finding in the heart-lung preparation increase of the peripheral resistance markedly enhanced the tendency to fibrillation.

The same phenomenon was observed in hearts *in situ* exposed to long lasting or repeated overstrain. The importance of these findings as to the pathomechanism of arrhytmias occurring in heart failure is discussed.

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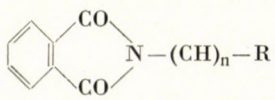
The N(ω-aminoalkyl)-phthalimide derivatives, a new group of compounds possessing antifibrillatory action

Starting out from the structure of procaine amide, a new group of antifibrillatory compounds has been synthetized. The N-(ω-alkylamine)-phthalimide derivatives differ from procaine amide mainly in that they contain no primary amino group on the aromatic ring and they contain imide instead of amide bond, thereby a new five-ring is formed.

Leaving the phthalimide radical intact, the effect of changes in the secondary amino group as well as in the length of the alkyl chain on the antifibrillatory activity of the derivatives has been studied.



n = 1 — 4
R = aliphatic or alicyclic secondary amino group

When the secondary amino group is dimethylamine, diethylamine or morpholino group, the compound shows no antifibrillatory activity, whereas substitution with piperidine results in a significant antifibrillatory activity. The increase of activity went parallel with the length of the alkyl chain, but at the same time the toxicity and hypotensive activity of the compound also increased. Substitution with piperazine increased the antifibrillatory activity but also toxicity.

The N-methyl piperidine compound containing four alkyl-groups in the chain proved to be 1.7 times as potent in auricular and 2.5 times as potent in ventricular fibrillation as quinidine, at the same time its toxicity was only 1.6 times higher as that of quinidine.

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The influence of iso-dihydroperparine (NoSpa) on the noradrenaline effect in animal experiments

In acute experiments involving 20 cats the influence of NoSpa on the increase in the blood pressure and ECG changes induced by noradrenaline has been studied. The cats were anaesthetized with chloralose and blood pressure was recorded kymographically from the right carotid.

In doses of 10 to 12 μg/kg, noradrenaline promptly increased blood pressure by 40 to 60 mm Hg and increased the amplitude of the pulse. In the ECG the T wave often turned negative in lead II or III (a sign of ventricular hypoxia). Partial or complete atrio-ventricular block, bundle branch block, extrasystoles, ventricular paroxysmal tachycardia, were also observed. A single intravenous injection or the infusion of 2 mg/kg of NoSpa caused within a few seconds a fall of blood pressure, a decrease of pulse amplitude and normalization of the above mentioned ECG changes. Previous administration of NoSpa could not prevent the noradrenaline effect, but repeated injections or infusions of NoSpa significantly increased the noradrenaline tolerance of the animals.

Histologic study showed marked capillary hyperaemia without serious myocardial stasis or haemorrhage. After 8 to 10 noradrenaline-NoSpa experiments necrosed fibres without finer structure could be found in many parts of the heart muscle.

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Hypophyseal-adrenal activity in combined human foetal tissue cultures

Human foetal hypophysis or adenohypophysis cultured in combination with adrenal tissue showed ACTH activity for a considerable number (8 to 16) of days, as assayed by daily paper-chromatographic determinations of the amount of hydrocortisone present in the medium.

If added when hydrocortisone production had already been falling for several days, ACTH invariably increased adrenocortical hormone production. Remarkably, it reached its peak not on the day of addition but two to four days later, although the culture had been washed daily and no fresh ACTH had been introduced.

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Effect on the serum properdin level of thymectomy and adrenocortical hormones

The endocrine mechanism influencing the activity of the properdin (P) system, one of the humoral factors of aspecific immunity, is poorly known. In the present study the influence on the serum P-level of thymectomy and adrenocortical hormones has been investigated, separately and in combination, in a total of 111 male Wistar rats, weighing on average 60 g.

The sera were tested for properdin activity by the zymosan test, according to CSEH and SZABÓ, on the 28th day following thymectomy or sham-operation.

As compared with the control value (17.9 U/ml), the properdin level was found to be significantly increased after thymectomy (31.2 U/ml).

In the thymectomized animals zymosan did not increase the serum properdin level.

There was a difference between the effects of the glyco- and mineralocorticoids.

In the thymectomized rats hydrocortisone [5 mg/animal/day, administered for 8 days] significantly increased the serum properdin level to 33.9 U/ml, while desoxycorticosterone acetate [1 mg/animal/day, for 8 days] decreased it to 10.5 U/ml.

In the controls hydrocortisone caused a slight rise, and DOCA no change, in the serum properdin level.

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The effect of chronic protracted water load on adrenocortical function in the rat

In earlier experiments it was shown that the aldosterone production of rat adrenal slices increased in hyposmotic medium and that in man urinary aldosterone output increased on prolonged water load. In the present series

of experiments the effect of chronic protracted water load on the functional state of the adrenal cortex has been studied. The rats were given daily 2.5, 5 and 10 ml of tap water through a gastric tube for five days. As controls, we used partly untreated rats and partly such as were given 5 ml of saline solution four times a day for five days. On the 6th day, after killing the animals by decapitation, the right adrenals were subjected to histologic examination, while the left adrenals were incubated for 2 hours by GIROUD's method and the quantity of corticosteroids produced *in vitro* was determined. Following the loads,and in dependence on the quantity of water administered, an increase was noted in the weight and aldosterone production of the adrenals. The zona glomerulosa showed histological signs of hyperfunction; the karyometric curve determined by the JAKOBJ-PALKOVITS method shifted toward higher values and the mean nuclear volume increased significantly. In the saline-treated group aldosterone production does not increase and the zona glomerulosa shows signs of atrophy. This tends to support our earlier hypothesis that the hyposmosis resulting from the water loads would stimulate adrenal aldosterone production.

SPÄT, A., SALIGA, MARGIT, STURCZ, J. and SÓLYOM, J.
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Effect of aldosterone on intestinal cation transport

The rate of Na and K absorption in the intestines may greatly influence the electrolyte metabolism of the organism. However, no direct and unequivocal evidence is available about the small intestinal effect of aldosterone, a hormone significantly influencing Na metabolism.

A solution of known Na and K contents was introduced into an ileum segment isolated *in situ* in adrenalectomized rats. In one group this solution contained Na or K isotope. The changes undergone by the intestinal contents in 15 minutes were examined. One group received prior to the absorption period aldosterone intravenously. After the 15-minute absorption period, the fluid found in the intestinal lumen was tested for Na and K by flame photometry and for radioactivity by means of a GM counter. It has been found that 2.5μg/100 g d,l-aldostrerone significantly increased the absorption of ^{24}Na, but had no effect on that of non-isotope Na and K.

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Simultaneous determination of total 17-hydroxycorticosteroids and pregnanetriol in human urine

A chromatographic method has been allowing the simultaneous separation of different steroids pregnanediol, pregnanetriol and 17-hydroxycorticosteroids. By means of this method pregnanetriol (5beta-pregnane-3alpha, 17alpha, 20alpha-triol) and the total 17-hydroxycorticosteroids were determined side by side in human urine. The extract obtained by enzymic hydrolysis was chromatographed on "Nymco" florisil column. The total 17-hydroxycorticosteroids could be separated in such a pure form that they could be determined directly from the eluate by the PORTER-SILBER method. The pregnanetriol eluate was purified on Al_2O_3 column, to remove foreign chromogens. The purified pregnanetriol was then determined by the H_2SO_4 colour reaction, by spectrophotometry at 400, 435 and 470 mμ.

The reliability of the method concerning the normal pregnanetriol and 17-hydroxycorticosteroid values is discussed. The urinary excretion of the above steroids was studied in 14 cases of Cushing's syndrome, in 6 cases of hypopituitarism, in 7 cases of hypadrenia and 2 of adrenogenital syndrome. The results obtained were comparable with those reported in the literature and were in harmony with the clinical pictures. The method is believed to be suitable for studies of 17-hydroxycorticosteroid and pregnanetriol excretion.

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Effect of posterior pituitary hormones on adrenocortical and ovarian progesterone secretion in the dog

In female dogs acute experiments have been made to study the effect of oxytocin and vasopressin on adrenocortical and ovarian progesterone secretion. Adrenocortical progesterone secretion parallel with corticoid secretion was assayed by paper chromatography.

Adrenocortical progesterone secretion was increased by 3 I. U./kg oxytocin or 1 I. U./kg vasopression. The increase of progesterone secretion went parallel with the increase in corticoid secretion. The same dose in the same animal was ineffective on ovarian progesterone secretion.

The results indicate that the regulation of adrenocortical progesterone secretion differs from that of ovarian progesterone secretion.

FENDLER, K. and TELEGDY, GY.
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Effect of chronic stress on neurohypophysial oxytocic and antidiuretic activity in the rat

Female albino rats were forced to swim until total exhaustion daily, for 29 days. The animals were divided into groups and were studied at 3 to 4 day intervals. Neurohypophysial oxytocic activity was assayed on the surviving rat uterus. Antidiuretic activity was determined on the basis of urine flow in the dog.

On the 6th and 8th days of swimming oxytocic activity was slightly decreased, but it was significantly increased on the 12th and 15th days. The increase, amounting to 4 to 7 times the control values, reached the maximum on the 18th day, then decreased from the 22nd to the 29th days, but the initial level was not attained during the period of observation. Pituitary antidiuretic activity likewise increased under the experimental conditions specified.

VÉRTES, MARIETTA and KOVÁCS, S.
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Effect of hypothalamic and posterior pituitary extracts and synthetic oxytocin on the TSH release and ^{32}P uptake of the anterior pituitary in vitro

The effect of hypothalamic and posterior pituitary extracts from dogs and rats, and of synthetic oxytocin on the TSH release and ^{32}P uptake of the dog's or rat's surviving anterior pituitary were examined.

All the three substances tested produced a significant increase in TSH-release and ^{32}P uptake of the anterior pituitary during the incubation period, as compared with the controls.

KOVÁCS, S. and VÉRTES, MARIETTA
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The effect of mesencephalic lesions and stimulation on pituitary-thyroid function

The results obtained after electrocoagulation or stimulation with chronic electrodes of certain mesencephalic areas in male albino rats may be outlined as follows.

1. Bilateral lesion damaging the anterior part of the mesencephalic reticular formation at the level of the nucleus ruber and a little dorsally to it, resulted in a significant increase of thyroid ^{131}I uptake.

2. In response to stimulation of the same area the ^{131}I uptake and release significantly decreased. This decrease was observed also in cortisone-treated animals.

3. Electrocoagulation more lateral and ventral than that described above, when the lesion affected the substantia nigra and pedunculus cerebri, caused no change in ^{131}I uptake, as compared with the controls. At the same time, the lesion was followed by permanent erection, and a highly significant increase in testicular and adrenal weight.

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Submicroscopic analysis of the adrenaline and noradrenaline secretion of the adrenal gland in different functional states

The physiological and submicroscopic changes of adrenaline and noradrenaline secretion and their correlations were studied under different stress effects. In rats swimming for 2 hours in water of 27°C the adrenaline content of the adrenal was reduced by 43 per cent, the noradrenaline content remained unchanged. Exposure to cold (0°C) reduced the noradrenaline content by 50 per cent, and the adrenaline content by 16 per cent. Insulin 10 U/100 g body weight decreased the adrenaline content by 42 per cent in 1 hour, and 81 per cent in 6 hours, accompanied initially by a 64 per cent increase of the noradrenaline content. After 6 hours the increase of noradrenaline content was merely 11 per cent, counted from the normal noradrenaline level.

The submicroscopic changes accompanying the above findings were as follows. In the adrenal medulla of the rat forced to swim the number of catechol granules (size, 100 to 175 mμ) decreased, while the number of large granules measuring 500 to 1000 mμ remained unchanged. A weaker electron absorption of the cytoplasm and the lamellar and vesicular dominance of the active Golgi system were characteristic. The cold effect caused hardly any reduction in the number of catechol granules, whereas markedly reduced it within 1 hour and caused a decrease in the electron absorption of the cytoplasm. At the same time, the large granules became dominating, together with the appearance of the active Golgi system and the lamellar, vesicular form of the ergastoplasm.

These observations are believed to be indicative of a close correlation between the two substances of the adrenal medulla and the changes in the two types of granule.

DOBOZY, A., MADARÁSZ, I., ZOLTÁN, Ö. T., OBÁL, F. and FÖLDI, M.
INSTITUTE OF PHYSIOLOGY AND SECOND DEPARTMENT OF MEDICINE UNIVERSITY MEDICAL SCHOOL, SZEGED

Factors influencing the gamma-aminobutyric acid level of the central nervous system

In the different structures of the central nervous system, well-defined gamma aminobutyric acid (GABA) levels, subject to certain physiological variation, but characteristic of the different structures, can be demonstrated by paper chromatography.

A parallelism has been established between the GABA concentration of the single structures and the excitability of the central nervous system.

In animal experiments, the authors succeeded in influencing the GABA content of the different cerebral structures and the excitability of the central nervous system. Hypoxia, insulin and clamping of the cervical blood vessels caused a decrease of the GABA level in every structure, whereas different alcohols increased the level, even after it has been lowered by the above mentioned treatments.

The significance of the biochemical factors involved in the metabolism of GABA has been discussed and conclusions have been drawn concerning the mechanism of the factors influencing the GABA level in cerebral tissues.

KOVÁTS, T. GY., VÉGH, P. and BÁLINT, G.
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The role of the autonomic nervous system in the endotoxin effect

The role of the autonomic nervous system has been studied in the THOMAS and SHWARTZMAN reactions elicited by means of endotoxin in rabbits and in blood pressure experiments in dogs, during the endotoxin effect. The haemorrhagic reaction (THOMAS reaction) which develops in rabbits in response to the intradermal injection of 50 to 100μg adrenalin combined with the intravenous injection of 50μg/kg endotoxin could be prevented by the local administration of dibenzylamine and enhanced by atropine. Dibenzylamine administered locally decreased also the SHWARTZMAN reaction. The two reactions cannot be considered identical, but in both of them the endotoxin exerts its action on the autonomic nervous system.

To study the effect of endotoxin on the autonomic nervous system, dogs under general anaesthesia were given 1 to 2 mg/kg endotoxin intravenously and the blood pressure was recorded. In agreement with the data in the literature, marked hypotension resulted. Following administration of endotoxin

10μg/kg adrenalin and 5μg/kg acetylcholine were administered alternately at 5 minute intervals. After 10 to 15 minutes the sensitivity to acetylcholine was strongly reduced, while that to adrenaline remained unchanged. The results tend to indicate that in the so-called adrenergic effect of endotoxin a blocking of the cholinergic mechanism may play a role, too.

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Renal oxygen consumption in different experimental conditions

The correlations between renal blood flow (RBF), tubular sodium reabsorption and renal oxygen consumption have been studied in anaesthetized dogs. In spite of the decrease of RBF having been accompanied by an increase of the arterio-venous oxygen difference, a positive correlation could be demonstrated between RBF and oxygen consumption. This means that the change in the arterio-venous oxygen difference was not sufficient for ensuring the stability of renal oxygen consumption.

A linear correlation could be demonstrated between tubular Na-reabsorption and oxygen consumption. After subtracting the so-called basal oxygen consumption, the reabsorption of 1 mEq Na is associated with the consumption of 0.57 ml of oxygen. Basal oxygen consumption varies in the different conditions, but the correlations between RBF, Na-reabsorption and oxygen consumption are identical under normal conditions, following clamping of the aorta, in osmotic diuresis, and in severe dehydration.

FORGÁCS, I. and BÁLINT, P.
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The function of the hydronephrotic kidney

By ligation of the left ureter, hydronephrosis was induced in dogs. Four or seven days later the function of this kidney was compared with that of the intact right one. The renal blood flow (RBF_{dir}) was found to have decreased to $^1/_3$—$^1/_4$ the normal, *i.e.* renal resistance increased. On the basis of the simultaneous analysis of arterial and venous blood and of the RBF_{dir}, it could be stated that in the hydronephrotic kidney glomerular filtration rate and tubular secretion only amount to fractions of the normal. Oxygen consumption is minimal in the hydronephrotic kidney; merely the so-called basal oxygen consumption is demonstrable.

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Mechanism of renal cortical necrosis induced by hormones

In previous studies it has been shown that in the kidney of rats pretreated with oestrone the administration of posterior pituitary extract (10 I. U. of Piton) caused extensive renal cortical necrosis of apparently hypoxic origin. As in that dose Piton alone did not cause renal damage it was obvious that oestrone rendered the kidney sensitive to the vaso-constrictive effect of Piton. This may happen in two ways.

1. Oesterone increases the sensitivity of the tubular epithelial cells to hypoxia;

2. it enhances the contraction of renal blood vessels.

To decide the problem, three series of experiments were carried out. The results were as follows.

1. The administration of oestrone did not aggravate the hypoxic tubular lesion induced by clamping the renal hilus.

2. In rats pretreated with oestrone, China ink injected into the aorta did not fill some of the renal blood vessels following the administration of *Piton*.

3. As determined by SAPIRSTEIN's method, the ^{86}Rb uptake of the kidneys (indicative of RBF) after Piton administration was significantly decreased in rats pretreated with oestrone. Oestrone and Piton above induced practically no changes.

The results indicate that oestrone sensitizes the renal blood vessels to the vasoconstrictive effect of posterior pituitary extracts. In this way severe hypoxia develops and the tubular epithelial cells undergo necrosis.

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Changes in renal function following acute renal lesion treated with procaine

In dogs with right nephrectomy a condition similar to the acute renal failure of humans has been induced by clamping the left renal artery for 2 hours. The animals died with uraemia in 3 to 7 days. When immediately after the arterial ligation the kidney was infiltrated with a ½ per cent solution of procaine, the animal survived. The difference in survival rate between the two groups was statistically significant.

RBF and V/min in the azotaemic animals were low, whereas in those treated with procaine they attained significantly higher values, identical

with the corresponding values found in normal animals having one kidney. Extraction of inuline and PAH, the measures of glomerular and tubular function, respectively, were likewise higher, but failed to reach the values obtained in normal animals with one kidney.

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Splanchnicotomy and the prevention of acute renal lesion in the dog

In dogs with unilateral nephrectomy a renal lesion corresponding to human acute renal failure has been induced by clamping the renal artery. The animals died in 3 to 7 days, with anuria and azotaemia. If the splanchnic nerves innervating the remaining kidney had been cut two weeks before ligating the renal artery, renal failure did not develop and after a transitory decrease of renal function and increase of NPN the animals survived in good condition. The difference in clinical condition and survival rate was significant between the two groups. While in the azotaemic animals severe cortical necrosis developed in the whole kidney, in the splanchnicotomized dogs cortical necrosis was limited to a small part of the organ. The results emphasize the role of neurogenic factors in the pathogenesis of acute renal lesions.

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Capillary filtration, stop-flow and renal lymph

In dogs with mannitol-induced diuresis, intravenous inulin was studied for its appearance in the renal lymph under stop-flow and free-flow conditions. The stop-flow period was continued for eight minutes. Inulin was injected $2\frac{1}{2}$ or 4 minutes after ureteral ligation. It appeared in the renal lymph within four minutes, both under stop-flow and free-flow conditions, and in concentrations about the same as in plasma. Given a high urinary inulin level, ureteral ligation failed to elevate the inulin concentration in the lymph of the kidney. Accordingly: 1. renal capillary filtration was not discontinued in the stop-flow period; 2. the tubules remained impermeable to inulin.

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Comparative analysis of the composition of urine, renal lymph and renal parenchyma

The Na concentration is lower in the renal hilar lymph than in the blood plasma or the capsular lymph. When the urinary electrolyte concentration is high, the electrolyte concentration of the cortical lymph is higher than that of plasma, while with dilute urine, the cortical lymph is more concentrated.

Occlusion of the renal lymphatics at unchanged GFR caused an increase in water and salt output. In sham-operated animals it could be shown that this is not due to a congestion of lymph, but to a "denervation polyuria".

The water, Na and Cl concentration of the renal medulla is higher, the K and protein concentration is lower, than that of the cortex. No significant correlation could be demonstrated between the relative electrolyte concentrations of urine, medullary and cortical parenchyma. There was a positive correlation between the inulin content of the urine and that of the medullar parenchyma.

Intravascular plasma volume values are 11.8 ml/100 g in the renal cortex, and 17.2 ml/100 g in the medulla; the total plasma protein space values are 22.3 ml/100 g and 32.8 ml/100 g, respectively. Clamping of the lymphatics for 24 hours, with the intravascular space unchanged, increased the total plasma protein space to 25.2 ml/100 g in the cortex and to 37.7 ml/100 g in the medulla.

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Effect of papaverine on the ^{86}Rb uptake of the isolated kidney

The changes in ^{86}Rb uptake of the isolated dog kidney in response to papaverine have been studied. The ^{86}Rb was injected directly into the renal artery and the activity of the outflowing blood was measured by means of a beta sensitive submerging GM counter. Renal ^{86}Rb uptake was calculated from the difference between the injected and outflowing activities.

It was found that in response to the simultaneous injection of 20 mg papaverine/min into the renal artery the renal ^{86}Rb uptake was reduced to one half — one third the control value.

Considering that papaverine has no direct influence on the ^{86}Rb uptake of tissues, it has been concluded that in response to papaverine some of the blood passes over directly from the arterial to the venous system of the kidney, by-passing the capillaries.

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Effect of papaverine on the accumulation of PAH and Na–K exchange in renal cortical slices

In dog experiments the administration of papaverine was found to decrease C_{PAH} and E_{PAH}, and to considerably increase the excretion of Na. The mechanism of these shifts has been studied in renal cortical slices.

At a concentration of 2×10^{-5} M, both at 37°C and 28°C, papaverine reduced the accumulation of PAH in the slices to about 50 per cent the control value. This concentration failed to influence O_2 consumption. With the increase of papaverine concentration, O_2 consumption began to decrease, and PAH accumulation continued to decrease. At a concentration of 10×10^{-5} M, papaverine reduced O_2 consumption to 56 per cent the control value and practically stopped PAH accumulation. Up to this concentration no change was noted in the concentrations of Na and K; when the concentration of papaverine was further increased, the concentration of Na increased and that of K decreased.

According to these data, papaverine seems to be potent in inhibiting certain active transport processes in the kidney (accumulation and secretion of PAH), without acting on O_2 consumption, whereas it influences some renal functions (Na and K transport) apparently only by inhibiting the oxydative processes. The natriuretic effect of papaverine does not seem to affect the electrolyte exchange of the tubular cells in general, but rather exerts an action on the Na-reabsorption cells of a given tubular area.

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Reliability of clearance tests following physical work

The mechanism of overstrain proteinuria has been studied by the clearance technique. In the same subjects, C_{creat} decreased by 35 per cent on swimming in water of 34°C, remained unchanged in water of 23°C, and increased by 53 per cent on swimming in water of 16°C. The results indicate that the change in C_{creat} depends not so much on the work performed, as on the temperature. It was attempted to supplement the observations with C_{PAH} determination during work. Rabbit and rat experiments were carried out to elucidate the mechanism of the observed low C_{PAH} values. The results have shown that PAH diffused into every tissue, depending on the blood supply of the organ. When the blood concentration decreased, it diffused back into the venous system with a shift in phase. Thus, if blood flow in some

organ changes during the clearance test, the C_{PAH} does not reflect renal blood flow; therefore, the C_{PAH} method is not suitable for the determination of RBF during muscular work, either.

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L'adaptation du cobaye aux constricteurs des voies respiratoires

L'adaptation physiologique est un phénomène qui s'établit progressivement sous l'influence répétée et prolongée des stimulants par lesquels les fonctions physiologiques ont été troublées. Cette nouvelle situation permet à l'organisme adapté de mieux tolérer une dose donnée de ces stimulants en modifiant au minimum sa régulation physiologique fondamentale.

Quelques aspects caractéristiques de cette transformation ont été étudiés en prenant comme critère l'adaptation du cobaye aux bronchoconstricteurs. L'adaptation à l'histamine (H) et à l'acétylcholine (Ach) a été provoquée par deux voies: aérienne et intrapéritonéale. Pour les aérosols, nous avons eu recours à un générateur décrit par DAUTREBANDE, appelé D-30, qui produit des particules exclusivement inférieurs à 0,5 μ en raison de plusieurs millions par ml d'air et qui, en raison de cette extrême dispersion, touchent rapidement toutes les formations réceptives du poumon. De plus, à cause de la stabilité dans l'air des aérosols produits, la dose dispersée est toujours semblable à elle-même par unité de temps.

Les résultats obtenus peuvent être résumés comme suit.

L'adaptation aux bronchoconstricteurs ne peut être obtenue qu'après séléction rigoureuse des doses appropriées d'H ou d'Ach. Ni les doses inférieures au seuil de la sensibilité ni les doses suivies d'un choc ne sont capables de provoquer l'adaptation. Cette observation liminaire permet sans doute d'expliquer le grand nombre d'opinion contradictoires trouvées dans la littérature.

Nous avons également observé que la dose génératrice d'adaptation dépend aussi de la sensibilité individuelle des animaux. Pour déterminer la dose susceptible de provoquer l'adaptation, il est donc indispensable d'éprouver la sensibilité de chacun des cobayes à chacun des agents bronchoconstricteurs étudiés.

Dans ce but, le procédé suivant a été adopté: pour des doses croissantes de H ou d'Ach, on mesure le temps des expositions, nécessaire pour produire un effet physiologique déterminé sur la fonction réspiratoire. On obtient ainsi une courbe de sensibilité (généralement hyperbolique) qui est absolument caractéristique pour chacun des cobayes étudies. D'après cette courbe, on peut donc choisir la dose optimale capable de produire l'adaptation dans chaque cas.

Toutefois, pour que l'analyse de l'adaptation soit possible et valable, il faut encore déterminer le degré de cette adaptation à des doses limites. A cet effet, nous nous servons d'une méthode qui permet de calculer la capacité d'adaptation en fonction du temps d'exposition et de la dose.

Cette méthode, décrit précédemment, nous a permis d'étayer la base principale de cette étude, à savoir qu'en dehors des limites de doses pré-établies, il est impossible non seulement de provoquer l'adaptation mais encore de la mesurer.

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Correlation between histamine and adrenaline metabolism

It has been shown by SCHAYER that in response to strong external stimulation the histidine decarboxylase activity and together with it the formation of histamine increased in the tissues of mice. He claimed that the mediator between stress and the enzyme was adrenaline, in view of histidine decarboxylase activity being increased by adrenaline.

In the present study it has been investigated whether an elevation of the histamine level would induce an increase in diaminooxidase (DAO) activity, which, by breaking down histamine, would restore homeostasis. Therefore, rats and dogs were treated with histamine and adrenaline and tested for DAO activity. It was found that both histamine and adrenaline increased DAO activity; the maximum increase was attained between 2 and 6 hours. Activity could be increased also by acetylcholine. The cholinesterase level behaved in the same way as DAO activity. In response to the administration of single doses of adrenaline or acetylcholine, activity increased significantly, but the reaction disappeared after repeated administrations. On chronic adrenaline or acetylcholine treatment a "phase of exhaustion" develops, the reaction cannot be elicited, or an inverse reaction is evoked. The reactions of the male animals differed somewhat from those of the females.

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Correlation between thyroid nucleic acid and iodine metabolism

It is generally accepted that the nucleic acids play a directing role in cellular metabolic processes of cells. It was therefore interesting to determine whether in the thyroid the highly specific hormone production could be brought into correlation with some specific RNA system.

The amount of RNA and DNA of the rat's thyroid were determined, the RNA—P content was found to average 70.3 μg/100 mg wet weight and the DNA—P content, 31.1 μg/100 mg wet weight, respectively. The RNA/DNA ratio varied from 1.8 to 2.5.

On labelling with ^{131}I *in vivo*, the ^{131}I activity of the thyroid homogenate estimated after different periods after administration showed different distributions in the fractions obtained by the SCHMIDT—THANHAUSER method. It was shown that the distribution of ^{131}I was subject to dynamic changes in the RNA and DNA + protein fractions, notably at first most of the ^{131}I activity was in the RNA fraction, while later this shifted in favour of the DNA + protein fraction.

In the early phase, the RNA system seems to play a role in the transport of iodinated amino acids. This may be in correlation with thyroglobulin synthesis.

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A study of elastase inhibitors of plant origin

Protein or polypeptid type inhibitors derived from potatoes and beans inhibited both the non-specific (caseinolytic) and specific (elastolytic) actions of elastase. The bean inhibitor also inhibited trypsin to a significant extent, while the potato inhibitor hardly showed any antitryptic effect. The antagonisation of the pharmacological effects of elastase was demonstrated in the following tests:

1. In rabbit aorta slices, incubated *in vitro*, the histologically detectable enzymic breakdown of the elastic fibres brought about by elastase is inhibited.
2. In the dog's carotid artery perfused *in situ* the inhibitor prevented elastase from widening the oscillogram.
3. Contractions of the isolated rat uterus caused by elastase was inhibited.
4. In mice the toxic effect of intravenously administered elastase could be antagonized by pretreating the animals with the inhibitor by the intravenous route.
5. In rats pretreated with the inhibitor by the intraperitoneal route, the intraplantar injection of elastase produced only a smaller oedema of the paw.

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The difference between priamid and atropine in their action of the experimental ulcer of the rat

Priamid R (2,2-diphenyl-4-diisopropylaminobutyramide methyliodide) was described in 1955, together with other 2,2-diphenyl-4-dialkylaminobutyramide derivatives. These compounds do not belong to the group of amino esters and are therefore broken down at a much slower rate in the organism. They have the further advantage that in spite of their quaternary amino group they are absorbed completely and evenly.

Animal experiments and clinical trials showed Priamid R to inhibit gastric ulcer about eight times more potently than atropine. The aim of the present study was to clarify the mechanism of this action.

Gastric ulcer was induced in rats by SHAY's method. In agreement with the data in the literature, the anti-ulcer action of Priamid R was found to be eight times stronger than that of atropine. The pupils showed no significant difference in mydriatic action between the two drugs.

According to the data in the literature, in man Priamid R inhibits the increase of gastric acid secretion caused by histamine. As tested by the method of HERR and PÓRSZÁSZ Priamid R in doses of 4.5 mg/kg, 3.0 mg/kg and 1.0 mg/kg, did not inhibit the increase of gastric acid secretion caused by histamine and its effect on the increase of gastric acid secretion caused by enterotonin was identical with that of atropine.

It has been concluded that the inhibitory effect of Priamid R on the development of gastric ulcer involved some further mechanisms in addition to the parasympatholytic action.

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Tetracaine, as a factor promoting drug absorption

Painting the oral mucosa, simultaneously with or before, the administration of tetracaine was found markedly to promote the absorption of drugs which otherwise are absorbed poorly (acetylcholine, histamine, adrenaline). For example, without tetracaine very high doses (30 mg/kg) of acetylcholine had to be used in concentrate (50 per cent) solution to be effective in the oral cavity, whereas with tetracaine treatment 0.5 to 1.0 mg/kg in dilute (0.5 per cent) solution sufficed. This effect of tetracaine is remarkably long-lasting; it is demonstrable, though in a reduced measure, even at 48 hours. Other local anaesthetics (cocaine, procaine, xylocaine, beta-eucaine, veratrine)

have no such effect. The absorption of the above drugs is not promoted by pretreatment with dilute acid, carbonate or KCN. Tetracaine also improves absorption from the rectal mucosa, too. Thus, the compound is capable of breaking through the barrier inhibiting the absorption of certain drugs without causing damage or lasting disturbance in the function of the absorbing surface. The tests were made in both ananaesthetized and unanaesthetized animals, absorption was estimated on the basis of changes in blood pressure.

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Pharmacological actions of chloro- and aceto-N-acyl-phenothiazine derivatives

New phenothiazine derivatives have been prepared in order to eliminate their untoward side effects on the CNS. The actions of these compounds can be modified by instituting changes in the R_2 side chain, linked to the position 2 $(R)_1$.

Therefore, the effects of certain new derivatives substituted at positions 2 and 8 were studied and compared with N-dimethylamino-acetil-phenothiazine (A) as the basic compound.

It has been found that:

1. Every derivative substituted at the positions 2 and 8 was 2 to 4 times less toxic than the basic compound.

2. 2-Cl-A as an analgesic, was 4 times more potent than amidazophene, 3 times more potent than 2-Cl-8-aceto-A and as potent as 2-Cl-8-iso-A in the rat.

3. The corneal anaesthetic potency of 2-Cl-A was comparable to that of cocaine in the guinea pig.

4. Substitutions at positions 2 and 8 had no significant influence on the potentiating effect of A on the anaesthetic properties of hexobarbital in the rat.

5. The antihistaminic effect of the derivatives was weaker, than that of the basic compound.

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New data to the pharmacology of the benzimidazole derivatives

The benzimidazole derivatives have a wide scale of pharmacological properties. There are convulsant, muscle-paralyzing and analgesic compounds among them. The present study deals with a strong analgesic compound, di-

methyl-aminoethyl-metoxy-benzyl-5-nitrobenzene imidazole, not analysed in detail before.

By the method of WOLFE and MACDONALD it was shown that on subcutaneous administration to mice the analgesic effect of the drug surpassed 56 times that of morphine. There was no difference in the duration of action between the two drugs. Habituation to the drug was three times as fast as that to morphine. Injected subcutaneously into rabbits, the drug reduced respiratory volume 71 times more effectively than morphine. N-allyl-normorphine, given together with the compound subcutaneously at a ratio of 1 in 20, reduced the analgesic effect to one-fourth and the respiratory volume decreasing action to one half. The 100 per cent analgesic dose slowed down the passage of carbon-dyed food through the small intestine of mice 1.12 times as effectively as morphine. Taking into account the doses, the drug was 37 times stronger than morphine in causing obstipation. As administered subcutaneously, the compound was only 1.36 times more toxic than morphine. In the toxicity tests mice behave exactly as those treated with morphine.

Accordingly, the compound is an analgesic similar in action to morphine, without possessing SCHAUMANN's analgiphoric group.

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^{59}Fe uptake of rabbit bone marrow erythroid cells in vitro: the energy dependence of the process

The bone marrow cells of proliferative ability can divide and differentiate *in vitro* and ^{59}Fe presents a suitable means for studying their differentiation.

The ^{59}Fe uptake of the rabbit bone marrow cells has been studied in a medium consisting of 20 per cent homologous serum in Tyrode's solution. The medium contained 10^7, nucleated cells/ml ^{59}Fe citrate was added. The ^{59}Fe activity of the cells was expressed as the ratio of the total impulse count administered and the activity taken up by the cells, related to the erythroid cell count.

It was found that the ^{59}Fe uptake by the cells depended on the temperature and was influenced by treatment with agents inhibiting fermentation and oxidation (F^-, dinitrophenol).

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Substances regulating myelopoiesis in vitro

The effect of sera from leucopenic, respectively, leucocytotic rabbits on normal rabbit bone marrow was studied *in vitro*. The rate of ^{14}C-formiate incorporation served for measuring the mitotic rate. Sera collected in the leucopenic phase or in the initial phase of leucocytosis, and incubated with normal bone marrow, were found to increase ^{14}C-formiate incorporation into cells significantly. On the other hand, sera collected at the peak of leucocytosis inhibited formiate incorporation. Bone marrow from control rabbits incubated with sera from leucopenic, leucocytotic animals respectively produced a characteristic change in the mitotic rate and in the ratio of myeloid precursors and mature myeloid elements. Kinetics of formiate incorporation qualitatively agreed when bone marrow from leucopenic, leucocytotic and control rabbits, respectively, was incubated with the animals' own sera, or when bone marrow from control rabbits was incubated with leucopenic and leucocytotic sera, respectively. It may be assumed that the agents considered represent the humoral system maintaining the homeostasis of myeloid elements.

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Effect of the tissue erythropoiesis stimulating factor (ESF) on the ^{59}Fe incorporation into the bone marrow, in vitro

In a previous study it was shown that under hypoxic conditions every tissue was able to produce ESF. In the present investigations the site of action of tissue ESF was studied. Two samples prepared from the same lung homogenate and saline, each of them containing fresh bone marrow from albino rats, served for carrying out the experiments. One of the lung tissue samples was previously kept under reduced pressure for 3.5 hrs, the other under atmospheric pressure (control). The effect was measured by the rate of ^{59}Fe incorporation into the erythroid elements of the bone marrow (0.5 μC/50—70 million cells). After incubation of the samples the incorporated iron was isolated and determined as hematin. ^{59}Fe incorporation into the saline and control samples, resp. was almost equal. On the other hand, the sample from the lung homogenate kept under reduced pressure incorporated by 69 per cent ($p < 0.01$) resp. 43 per cent ($p = 0.02$) more of ^{59}Fe than did the saline and control samples resp.

The results indicate that hemoglobin synthesis in the bone marrow is increased by pulmonary ESF which exerts the same effect as serum ESF. This experimental system is believed to be suitable for determining the different tissue ESFs.

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Effects of anticholinesterases on potassium permeability of frog muscle

For the measurement of steady state membrane potentials and the ^{42}K fluxes, whole sartorius muscles were dissected from the frog. For the measurements concerned with the rapid changes in potential resulting from rapid changes in the composition of the external medium, bundles of 4 to 20 fibres were dissected from the semitendinosus muscle of the frog. Muscle membranes depolarized to a new steady level when placed in Ringer's fluid containing 2.5 mM K to which 0—5 mM eserine had been added. The depolarization from the normal level, —92 mV, was linearly related to the eserine concentration. In the presence of 1 mM eserine, fibres initially depolarized less when $[K_0]$ was increased and depolarized more when $[Cl]_0$ was reduced than when eserine was absent. The rate constant for ^{42}K loss was reduced to about 58% and 35% of its normal value in the presence of 1 mM and 2.5 mM eserine, respectively. The eserine effect was reversible. Neostigmine had no such effect even at a concentration of 10 mM. These data show that eserine reduced the resting membrane permeability to K.

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Ion transport in tonic and tetanic muscles

Cats under hexobarbital anaesthesia were subjected to bilateral nephrectomy. Then hypertonic NaCl solution was infused intravenously and the effect of the increase of extracellular NaCl concentration on the mechanical and electrical phenomena of the tetanic gastrocnemius and the tonic soleus muscle was studied. When the extracellular NaCl concentration was as high as 180 to 250 mEq/litre the tetanic muscle responded neither to direct nor to indirect electrical stimulation. At the same time, size and shape of the action potentials recorded from the muscle showed hardly any change. Under similar conditions, the mechanical and electrical responses of the tonic muscle were unchanged.

Next, the effect of denervation on the tonic and tetanic muscles of rats was studied. It was found that after denervation the Na^+ concentration increased in the tetanic and decreased in the tonic muscles. The changes of K^+ concentration were less distinct; in both types of muscle a decrease was observed in the early phase of denervation. While the passive Na uptake of tetanic muscle decreased, that of the tonic muscle increased, most markedly when the hypersensitivity following denervation had developed.

The experiments elucidate from a new standpoint the functional and biochemical differences between the two types of muscle.

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The effect of inactivity on the metabolism of tonic and tetanic muscles

In earlier studies, several differences have been shown to exist in the metabolism of tonic and tetanic muscles. In the present investigations, the effects of denervation and inactivity on the metabolism of the two types of muscle have been studied. Inactivity was ensured by unilateral denervation or by immobilization by splints.

After denervation, O_2 uptake decreased in the tonic muscle and increased in the tetanic muscle. During the first week the glycogen content slightly decreased in the tonic, and slightly increased in the tetanic muscle. Seven to ten days after denervation the glycogen content increased in the tonic muscle, and decreased in the tetanic one. At the same time, the tonic muscle began to show atrophy. During the 2 weeks of observation the tetanic muscle showed only slight, or no, atrophy. Aerobic lactate and pyruvate production in the tetanic muscle changed almost parallel with the change in glycogen concentration; during the first week an increase, later a steep fall occurred. In the tonic muscle the glycogenolytic activity first decreased, later increased in response to denervation, but the aerob lactate production did not reach the rate recorded in the tetanic muscle. The high energy phosphate content usually increased in both types of muscle. The inorganic P level underwent similar changes.

Immobilization induced essentially identical changes. However, during the 2 weeks of observation inactivity alone produced no such unequivocal alterations in O_2 consumption, as denervation did.

The results indicate that the metabolism of the two types of muscle influenced by inactivity is different.

The evidence obtained might be of value in the chemical analysis of neurogenic and myogenic muscle diseases.

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Muscle co-ordination during spreading the fingers and grasping

The activation and desactivation of the muscles of the hand and forearm were examined by recording the action potentials during spreading the fingers, as a preparatory movement, and the subsequent grasping of the dynamometer. When the fingers are spread, the extensor digitorum communis muscle is activated first, and only in a small number of cases the superficial flexor digitorum, but the potentials of the latter are always significantly lower than those of the extensor. The activity on the extensor lasts longer, but that of the flexor is also clearly demonstrable. Desactivation, in contrast to activation, usually begins in the flexor muscle, less often in the extensor, and occasionally in both. Grasping the dynamometer with 20 kg force is accompanied by a dominance of extensor activity. This begins sooner and its activity lasts longer than that of the flexor, but its innervation ceases earlier.

The observations indicate that the flexor activity during spreading the fingers serves gradation, and therefore, instead of antagonism, it should be regarded as a modulator effect. This is particularly conspicuous in the extensor muscle, when the dynamometer is being grasped. This muscle serves also as a fixator, and the profundus co-operates with the superficial flexor digitorum. The different activation patterns observed in some cases suggest that the movement pattern shaped in higher structures obtains its final form in the peripheral motor structures.

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Thin layer chromatography of lipids and corticosteroids

A Demonstration

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Adaptation of glucose-6-phosphatase in the liver

It is well-known that in the liver the last step of blood sugar production is catalyzed by G-6-P-ase, which splits G-6-P into glucose and inorganic phosphate. According to the literature, fasting or the feeding of protein and fat increase the activity of G-6-P-ase. The activity of the enzyme increases in diabetes, too. It has been shown that feeding of carbohydrate significantly reduces hepatic G-6-P-ase activity. This suggests that fasting or the feeding of

protein and fat do not by themselves increase G-6-P-ase activity, but the cause of the increase is a lack of the inhibition resulting from feeding carbohydrate.

Feeding pure carbohydrate decreases G-6-P-ase activity, but this decreases also when protein and fat are given together with the carbohydrate. If carbohydrate is omitted from the diet, the activity markedly increases.

Experiments are in progress to determine whether an inhibition of the enzyme, or a decrease of enzyme production is responsible for the decrease in activity caused by feeding carbohydrate. Adrenaline, administered during carbohydrate feeding while the glycogen content of the liver is high, increased the G-6-P-ase level. It may be assumed that the G-6-P formed from glycogen, as a substrate of G-6-P-ase, induces the production of the enzyme. Experiments are in progress to study the effect of insulin administered in the course of carbohydrate, protein and fat feeding.

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The influence of drugs on the CCl_4-induced cirrhosis of the liver in the rat

Male albino rats were treated with 0.1 ml/100 g CCl_4 twice weekly over 16 to 30 weeks.

By the end of the experiment the hydroxyproline content of the liver increased to 4—5 times the initial value. Glutaminc-oxalacetic acid transaminase activity of serum was increased. The bromosulpholein test indicated liver lesion. The calcium content of the liver was doubled, the potassium concentration was slightly decreased, the sodium content remained unchanged.

Tolbutamide (0.2 per cent in the food), methionine (0.2 per cent in the food), Oradian (N_1-(4-chlorobenzenesulfonyl)-N_2-cyclohexylurea, 0.2 per cent in the food), acetylhomocysteinethiolactone (500 mg/kg, subcutaneously, twice a week), hydrocortisone (30 mg/kg subcutaneously, twice a week) decreased the collagen content of the liver.

Choline (0.25 per cent, in the food) had no liver-protecting action.

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Effect of X-ray irradiation on liver regeneration

Total body irradiation with 500 r definitely reduced the weight of the liver regenerate. This inhibitory effect can be prevented by the administration of bone marrow and splenic cell suspension. Irradiated bone marrow and splenic

cell suspensions have no such protective effect. The next step, carried out for the sake of completing the experiment, brought the following remarkable evidence. Irradiated bone marrow and splenic cell suspensions were injected into non-irradiated, partially hepatectomized rats. The irradiated splenic cell suspension inhibited the regeneration of the liver slightly, whereas the irradiated bone marrow suspension inhibited it significantly. Irradiated suspensions of muscle, liver, embryonic liver, leucocytes and erythrocytes, as well as irradiated blood had no such effect. It is well-known that on irradiation so-called radiotoxins are formed in the tissues. It remains to be seen whether in the case of the irradiated bone marrow a particularly strong radiotoxin, or eventually some other substance is responsible for the effect.

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Calcium regulation of teleostei

The calcium metabolism of *Cyprinus carpio* was studied in chronic experiments, by changing the calcium content of the environment. In hypocalcic surroundings the serum calcium level decreased fast but later became normal. In hypercalcic medium the serum calcium level increased slowly. The results indicate that the serum calcium level does not depend exclusively on the calcium content of the medium.

The existence of active regulation is supported by the fact that hypocalcaemia evoked by EDTA is compensated by the organism.

According to further results, the gills play an important role in the regulation and exchange of calcium between the organism and the environment, both as calcium adsorbents and calcium depots.

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Reflex studies on the visceral ganglion of Anodonta cygnea L.

Various branches of the isolated visceral ganglion of *Anodonta cygnea* were stimulated with square pulses and the action potentials recorded from other nerves of the ganglion were studied. The influence of various drugs on these action potentials was also investigated.

The nervous pathways studied were, 1. cerebrovisceral connectivum $\rightleftharpoons$ $\rightleftharpoons$ muscle nerves, 2. cerebrovisceral connectivum $\rightleftharpoons$ mantle nerve; 3. unilat-

eral cerebro-visceral connectivum $\rightleftharpoons$ contralateral connectivum. In every case the action potentials had several, distinct components.

The drugs applied were, nicotine, atropine, hexamethonium, TMA, TEA and chlorpromazine. Treatment of the visceral ganglia with atropine, hexamethonium and TMA partly abolished the evoked action potentials in the investigated pathways. In the case of nicotine, TEA and chlorpromazine not only the transmission through the visceral ganglion was inhibited but also in the nerves themselves.

The results indicate that the impulse-transmission through the visceral ganglion is partly cholinergic but thepe may be also pathways, where the transmission is either not cholinergic, or there is no transfer and the fibres traverse the ganglion without interruption. It seems, that nicotine, TEA and chlorpromazine destroy the function of the nonmyelinated nerves in *Anodonta*.

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